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Quantitative assessment of secondary white matter injury in the visual pathway by pituitary adenomas: A multimodal study at 7 Tesla MRI

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Abstract

OBJECTIVE—The objective of this study was to investigate microstructural damage caused by pituitary macroadenomas by performing probabilistic tractography of the optic tracts and radiations using 7-T diffusion-weighted MRI (DWI). These imaging findings were correlated with neuro-ophthalmological results to assess the utility of ultra-high-field MRI for objective evaluation of damage to the anterior and posterior visual pathways.

METHODS—Probabilistic tractography employing 7-T DWI was used to reconstruct the optic tracts and radiations in 18 patients with adenomas and in 16 healthy volunteers. Optic chiasm compression was found in 66.7% of the patients and visual defects in 61.1%. Diffusion indices were calculated along the projections and correlated with tumor volumes and results from neuro-ophthalmological examinations. Primary visual cortical thicknesses were also assessed.

RESULTS—Fractional anisotropy was reduced by 21.9% in the optic tracts ($p < 0.001$) and 17.7% in the optic radiations ($p < 0.001$) in patients with adenomas. Patients showed an 8.5%

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increase in mean diffusivity of optic radiations compared with healthy controls ($p < 0.001$). Primary visual cortical thickness was reduced in adenoma patients. Diffusion indices of the visual pathway showed significant correlations with neuro-ophthalmological examination findings.

CONCLUSIONS—Imaging-based quantification of secondary neuronal damage from adenomas strongly correlated with neuro-ophthalmological findings. Diffusion characteristics enabled by ultra-high-field DWI may allow preoperative characterization of visual pathway damage in patients with chiasmatic compression and may inform prognosis for vision recoverability.

Keywords

Pituitary adenoma; visual pathway; ultra-high field MRI; neuro-ophthalmology; tractography; neurosurgery

1. Introduction

Pituitary adenomas are common lesions with an estimated prevalence of 15% and 23% in the general population according to autopsy and radiological studies, respectively¹⁴. Proximity to the suprasellar cistern makes visual field defects (VFDs) common symptoms of macroadenomas that outgrow the sella^{7,17,26}. While surgical decompression of the optic chiasm is a well-established treatment to improve vision, only a minority of patients will experience symptoms requiring surgical intervention^{22,23}.

Clinical assessment of optic nerve and/or chiasm compromise is achieved by conventional magnetic resonance imaging (MRI) and neuro-ophthalmological examination²³. Clinical MRI may be used to determine tumor size and position relative to the optic apparatus, however, it cannot probe microstructure²³. Neuro-ophthalmological exams are similarly limited in that they are unable to assess damage to posterior optic structures, such as the optic radiations, and assessment are somewhat subjective. Diffusion-weighted magnetic resonance imaging (dMRI) may help overcome these limitations by characterizing the integrity of white matter microstructure *in vivo*²¹. Few previous studies have employed dMRI to measure microstructural integrity of the visual apparatus in the presence of adenomas^{3,23,28}. Those studies have focused almost exclusively on anterior structures, commonly reporting reduced fractional anisotropy (FA) and increased mean diffusivity (MD) of the optic nerves and chiasm^{3,23,28}.

The primary objective of this study is to investigate microstructural damage caused by pituitary macroadenomas by performing probabilistic tractography of the optic tracts and radiations. To our knowledge, this is the first study to acquire diffusion indices of these structures using the high spatial resolution afforded by 7 Tesla MRI. Microstructural alterations in the optic tracts and/or radiations may serve as an objective marker to inform surgical planning. Furthermore, since approximately 20% of patients that undergo surgical decompression of the optic chiasm do not achieve appreciable improvement in visual function²⁰, high-resolution dMRI may help predict which patients are likely to respond favorably to surgery in advance of their procedures.

We secondarily used high-resolution structural MRI to quantify cortical thickness of the primary visual cortices and optic nerve sheath diameters (ONSD) to identify any association with macroadenomas. While reduced thickness of the cortical ribbon has been observed in conditions that affect vision, such as glaucoma^{6,16}, changes in cortical thickness have not been reported in patients with macroadenomas. Similarly, ONSD is known to increase as a result of elevated intracranial pressure¹⁵, but it is unknown whether the nerve sheath is affected by suprasellar lesions. These anatomic measurements may supplement microstructural findings in the visual pathways and help better characterize secondary damage to the visual pathway from adenomas.

2. Methods

2.1 Participants

Eighteen patients [8 females, mean age 44.6 years, standard deviation (SD) 13.4 years; 10 males, mean 49.9 years, SD 11.0 years] with pituitary macroadenomas that were scheduled for transsphenoidal surgery were recruited through their neurosurgeon (RS) at the Mount Sinai Medical Center. 16 of the patients were age- and gender-matched with 16 neurologically and psychiatrically healthy controls [8 females, mean 42.1 years, SD 12.9 years; 8 males, mean 45.5 years, SD 5.9 years]. Each participant provided written informed consent prior to the study.

2.2. Imaging Protocol

Participants were scanned under an Institutional Review Board-approved protocol using a 7 T whole body scanner (Magnetom, Siemens Healthcare, Erlangen, Germany). A SC72CD gradient coil was used ($G_{\max} = 70$ mT/m, max slew rate = 200T/m/s), with a single channel transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA, USA). Scanning included a T_1 -weighted MP2RAGE sequence with the following parameters: TE(ms) = 5.1, TR(ms) = 6000, TI(ms) = 1050(3000), flip angle (FA) = $5^\circ(4^\circ)$, field of view (FOV) = 240×320 -mm², slices = 240, resolution = 0.7-mm³ isotropic, scan time (min) = 7:26. Quantitative T_1 -maps were derived from the MP2RAGE sequence. A coronal-oblique T_2 -weighted turbo spin echo (T_2 -TSE) (TE = 69, TR = 6900, FA = 150° , FOV = 202×202 mm², in-plane resolution 0.4×0.4 -mm², slice thickness = 2 mm, slices = 40, time = 6:14), and high-angular-resolved diffusion-weighted imaging (HARDI) dMRI ($b = 1200$ mm²/sec, TE = 67.6, TR = 7200, resolution = 1.05 mm isotropic, in-plane acceleration R = 3 (GRAPPA), reversed phase encoding in AP and PA directions for paired acquisition in 68 directions, total acquisition time = 20) sequences were acquired. The dMRI-processing pipeline included skull-stripping, eddy current correction using FMRIB Software Library (www.fmrib.ox.ac.uk/fsl), and correction of gradient non-linearities.

2.3. Tractography

MR images were analyzed on an in-house workstation. Three regions of interest (ROIs) were manually defined to perform tractography. The optic chiasm was traced on coronal T_2 -TSE images. The lateral geniculate nuclei (LGN) were marked on the coronal quantitative T_1 -maps. Manually defined ROIs were verified by a CAQ neuroradiologist (BD). Automated cortical segmentation was completed on the T_1 -weighted images with FreeSurfer image

analysis suite version 6.0 (<http://surfer.nmr.mgh.harvard.edu>). The pericalcarine and cuneus regions were extracted from the whole-brain segmentation and fused to create the ROI of the primary visual cortex (V1). ROIs were co-registered with the dMRI images using Statistical Parametric Mapping 12 in MATLAB (r2017a, The MathWorks, Natick, MA). Constrained spherical deconvolution and probabilistic tractography were performed using MRtrix3 (Brain Research Institute, Melbourne, VIC, Australia). The optic chiasm ROI was used as the seedpoint and the LGN were used as the endpoints to reconstruct the optic tracts. To include potentially damaged fibers, the default FA threshold of 0.1 and a maximum fiber angle of 50° were used for the optic tracts. The LGN were used as seedpoints and the primary visual cortices as the endpoints to reconstruct the radiations. The same FA threshold of 0.1 was used, but a maximum fiber angle was increased to 90° to ensure inclusion of sharply angulated fibers through the anterior deflections of the radiation called Meyer's Loop²⁵. Fibers failing to pass through both seedpoint and endpoint were rejected. Diffusion indices were calculated along the optic tracts and radiations at 20 equidistant points. A diagram of the human visual pathway and the ROIs used to perform tractography are shown in Figure 1.

2.4 Structural Measurements

Tumor boundaries were manually traced on each coronal T₂-TSE image using Osirix version 9.0.2 (Pixmeo, Geneva, Switzerland). Tumor volumes were calculated by summing the product of each cross-sectional area of tumor and slice thickness.

The net center deflections of the optic chiasm were measured by an experienced neuroradiologist (BD). The reference line of the chiasm was drawn by connecting the lateral-most aspects of the chiasm on either side in the coronal plane corresponding to the maximal chiasmatic deflection. From this plane perpendiculars were projected to the upper and lower margins of the chiasm at the point of greatest deflection, with the average of these values representing the greatest deviation of the central chiasm. Positive values reflect superior deviation and negative values inferior deviation.

Visual cortex thickness was measured using an automated FreeSurfer algorithm to find the average shortest distance between the pial surface and the white matter boundary on the T₁-weighted images. The cortical thicknesses of the pericalcarine and cuneus regions were averaged to yield V1 thickness.

ONSD was measured in Osirix using T₂-TSE axial images, at the slice providing best visualization of the optic nerves. The retrobulbar region was zoomed to 500x to facilitate caliper placement and diameters were measured 3 mm posterior to the ocular globe on an axis perpendicular to the optic nerves. Two observers blinded to each other's measurements performed independent assessments of the ONSDs, and their measurements were averaged.

The structural measurements collected in this study are shown in Figure 2.

2.5 Neuro-ophthalmological Examination

9 of the patients in this study underwent neuro-ophthalmological examination prior to surgery. Neuro-ophthalmologic evaluation included the completion of visual field by

Humphrey Visual Field Analyzer and optical coherence tomography (OCT) by Zeiss Cirrus HD-OCT or Heidelberg Spectralis SD-OCT. OCT was used to survey retinal nerve fiber layer (RNFL) in micrometers and Humphrey perimetry 30-2 or 24-2 visual field testing was used to determine the presence of visual field defects and calculate the mean deviation and pattern standard deviation (PSD). The reliability criteria used were fixation losses less than 30%, as well as false positive and false negative errors less than 30%. Ocular examination included slit lamp and dilated fundus examination.

2.6 Group Comparisons

To test for group differences, 16 patients (mean age: 44.9 years, SD: 9.8 years) with adenomas and 16 age- and gender-matched controls (mean age: 43.8 years, SD: 9.9 years) were compared. All statistical analyses were done using SAS v9.4 (SAS Institute Inc, Cary, NC). Independent-samples t-tests (two-tailed) were used to assess group differences between mean diffusion indices of the optic tracts and radiations in patients and controls. With two diffusion indices in the optic tracts and radiations, we therefore set our significance threshold to a Bonferroni-adjusted 0.0125.

We also compared V1 thickness, average thickness of the entire cortex, ONSD, and chiasm deflection in adenoma patients and controls. Two-tailed independent sample t-tests with a Bonferroni-adjusted p -value threshold of 0.0125 were used.

2.7 Correlation Analyses

Of the 9 adenoma patients undergoing Humphrey Visual Field Analyzer testing, 7 also received OCT testing. Pearson's correlation coefficient and corresponding p -values were calculated to determine associations between diffusion indices of the visual pathways and neuro-ophthalmological results. Diffusion and neuro-ophthalmological data were averaged across left and right hemispheres/globes because the optic tracts and radiations receive projections from both retinas. Pearson's correlation coefficients were also used to examine tumor volume and diffusion indices in the visual pathway. Because we analyzed three neuro-ophthalmological results, we accounted for multiple comparisons using a False Discovery Rate (FDR)-adjusted p -value. Pearson correlations with p -values at or below 0.05 after FDR correction were considered significant.

3. Results

The 18 patients diagnosed with adenoma and 16 healthy controls included in this study are summarized in Table 1. Diffusion-weighted images of sufficient quality were acquired for all participants, and the reconstructed projections agree well with known anatomy. Neuro-ophthalmological data was available for 9 of the adenoma cases.

3.1 Chiasmal compression

The optic chiasm was evaluated in 16 patients and 16 age- and gender-matched controls. The center chiasmal deflection in pituitary adenoma patients ($M = 2.58$ mm, $SD = 3.88$ mm) was significantly greater than in controls ($M = -0.11$ mm, $SD = 0.31$ mm), $p < 0.001$. We also found significantly reduced mid-chiasm thickness in patients ($M = 1.43$ mm, $SD = 0.74$ mm)

compared with controls ($M = 2.3$ mm, $SD = 0.55$ mm), $p < 0.001$. The correlations between adenoma volume and neuro-ophthalmology are shown in Table 2. Tumor volume positively correlated with PSD ($r = 0.89$, $p = 0.004$).

3.2 Diffusion Indices of the Optic Tracts and Radiations

Probabilistic tractography and diffusion characteristics for 16 adenoma patients and 16 matched controls are presented in Figure 3. The reconstructed projections showed good agreement with known anatomy. We plotted diffusion indices of the tracts and radiations on a spatially normalized axis to evaluate abnormalities along the anatomic trajectories (Figure 4). In general, we observed that patients and controls exhibited similar spatial patterns of diffusion characteristics among tracts and radiations. However, FA and MD patterns differed between patients and controls. The averaged FA of tracts and radiations was significantly lower in patients compared with controls. Likewise, the MD of the left and right optic radiations was significantly increased in patients compared with controls, however, MD in the optic tracts was not significantly different (Table 3).

Associations between diffusion indices in the visual pathway and neuro-ophthalmology were determined using Pearson's correlational coefficients (Table 3). Pearson's correlational coefficients were also used to assess relationships between diffusion indices in the visual pathway and tumor volume (Figure 5).

3.3 Structural Measurements

ONSDs were measured in 16 patients and 11 controls. The ONSD measurements collected by the two independent observers had an intra-class correlation (ICC) of 0.90 (left), and 0.88 (right), and an average ONSD ICC of 0.95. Adenoma patients exhibited significantly greater bilateral ONSD than controls (Table 3).

Cortical thickness of both left and right V1 was significantly reduced in adenoma patients. However, whole-brain cortical thickness did not significantly vary between patients and controls (Table 3).

4. Discussion

In this study, diffusion indices of the optic tracts and radiations were shown to differ significantly between patients with adenomas compared and healthy controls. These diffusion indices also correlated with the severity of neuro-ophthalmological impairment. Reduced FA and increased MD in the visual pathway appear to correlate with downstream damage from chiasmal compression, perhaps from demyelination and/or axonal degeneration. We also found reduced cortical thickness in V1 and increased ONSD in adenoma patients, providing further evidence of secondary pathology from pituitary adenomas in otherwise normal-appearing structures.

Chiasmal Compression and Visual Impairment

The strong positive correlation demonstrated between tumor volume and PSD suggests that with chiasmatic compression from enlarging adenomas, effects from localized VFDs

become more severe. PSD is the degree of difference between the measured visual field pattern and the normal pattern (“hill”) of vision³⁴. Larger PSD values indicate an increasingly irregular visual field pattern, signifying localized sensitivity loss³⁴.

Few studies have explored the relationship between tumor volume and quantitative ophthalmological scores. Lee et al. found that pituitary tumor volume positively correlated with PSD and negatively correlated with mean deviation²². Mean deviation is the average of the difference from the age-adjusted normal value at various test-points, representing the overall visual field depression³⁴. As mean deviation becomes more negative, the overall visual field worsens. Normal mean deviation values in healthy individuals range from 0 dB to -2 dB³⁴. While we did observe a negative correlation between tumor volume and mean deviation, this effect was not significant after correction for multiple comparisons ($p = 0.056$).

The RNFL is an area of the retina that contains axons of the retinal ganglion cells¹. Topographic alterations of the RNFL indicate changes in the integrity of the retinal ganglion axons of the optic nerve²⁸. The negative correlation we calculated between tumor volume and RNFL was not significant.

Disordered Diffusion Indices in the Optic Tracts and Radiations

We found significantly reduced FA in bilateral optic tracts and radiations of adenoma patients (Table 3). FA is the most commonly reported diffusion index, and reflects the degree of directional water movement within tissues^{21,31}. FA is considered to be a marker of microstructural integrity, and diminished FA is a non-specific marker of many neurological diseases^{21,31}. The mechanism for FA reduction may lie in trans-synaptic degeneration (TSD), the process through which direct injury to neurons results in degeneration of neurons with which they synapse¹². Secondary pathology has been reported in the visual pathways in conditions that cause primary damage to anterior optic structures such as glaucoma^{6,16} and optic neuritis^{29,32}. TSD in the optic tracts^{23,27} and radiations⁹ has been reported in a small number of suprasellar lesion studies, indicating anterograde TSD (aTSD, or Wallerian degeneration) in the distal visual pathway resulting from chiasmal compression.

Lilja et al. found a significant negative correlation between FA of the optic tracts and degree of VFD in patients with pituitary adenomas, but did not observe group differences in FA or MD of the tracts between patients and controls²³. However, similar to our results, Paul et al. found reduced FA in of the optic tracts resulting from chiasmal compression²⁷. Few studies have investigated changes in the posterior visual pathways resulting from adenomas, and to our knowledge there is only one reported attempt to characterize diffusion indices in the optic radiations of adenoma patients. Similar to our study, Phal et al reported reduced FA and increased MD of the optic radiations in patients with visual impairment caused by chiasmal compression²⁸. Interestingly, we observed bilaterally increased MD in the optic radiations but not in the optic tracts. Since MD is a direction-independent dMRI scalar that indicates the overall degree of water movement within a voxel, higher MD values commonly reflect damage to myelin or axonal membranes that reduce barriers to water molecule diffusion²⁴. While increased radiation MD was reported by Phal et al²⁸, it is somewhat unexpected that an analogous effect was not observed in the tracts, considering their

proximity to the site of chiasmal compression. Future investigation is required to validate this finding and establish a mechanism by which the radiations exhibit disordered MD while the tracts do not.

While these studies provide some corroboration of our findings, they employed dMRI at considerably lower resolution (at least 2mm isotropic). The large voxel sizes likely enhanced partial volume averaging effects, especially between the optic tracts and the surrounding cerebrospinal fluid¹¹, which may explain why some of our effects have not been found in earlier studies at lower field strengths.

We found that tumor volume positively correlated with MD in both the optic tracts and radiations (Table 2). This suggests that larger lesions with greater chiasmal compression cause greater downstream damage to both tracts and radiations. Optic tract FAs correlated significantly with tumor volume indicating a negative relationship between tumor volume and white matter integrity in the anterior visual pathway. However, a similar correlation was not found in radiations, suggesting an attenuated effect of lesion volume on myelin integrity in the posterior visual pathway.

Relationship Between Diffusion Indices and Neuro-ophthalmology

In this study, FA of the optic tracts positively correlated with mean deviation, so that less negative mean deviation scores correlated with increasing tract FA values. Optic tract FA negatively correlated with PSD, indicating that reduced white matter integrity of the optic tracts is associated with greater localized VFD impairment. No significant relationships were found between FA of optic radiations and neuro-ophthalmological results.

We found a significant positive correlation between MD of the tracts and PSD, as well as a significant negative correlation with mean deviation. These results suggest that axonal damage and/or demyelinating processes in the tracts may contribute to both localized and overall visual field depression in adenoma patients. MD of the radiations also showed a positive correlation with PSD, implicating the posterior visual pathway in localized vision loss.

To our knowledge, ours is the first study to correlate mean deviation and PSD with diffusion indices of optic tracts and radiations. While these findings further characterize the functional impact of suprasellar lesions on vision function, validation of our preliminary results in a larger cohort will be important and is an area continued investigation.

Thinning of the Primary Visual Cortex

We found significant thinning in bilateral V1 in patients with adenomas, with 6.4% reduction in cortical thickness on the left and 9.3% loss on the right. To determine whether these effects reflected a global cortical thinning, the mean thickness of the entire cortex was also assessed, however, no significant effect was observed. These results suggest localized degeneration in V1 in patients with chiasmal compression.

Regional thinning of V1 has been observed in various ocular diseases, including glaucoma^{6,16,30} and macular degeneration⁹, suggesting aTSD is characteristic of conditions

that primarily affect anterior structures in the visual pathway, such as the globe. In addition, Balk et al. found evidence of aTSD in multiple sclerosis patients with comorbid optic neuritis, correlating significant axonal loss in the optic nerve with severe neuronal atrophy in the V1⁴.

Our finding of V1 thinning may reflect aTSD in patients with adenomas. Alternatively, V1 thinning could be indicative of neural plasticity, and result from diminished visual stimuli from VFDs⁸. While reduced thickness of V1 has been reported in a number of different ocular diseases^{4,6,9,16,30}, ours is the first study to report V1 thinning in patients with suprasellar lesions.

Optic Nerve Sheath Diameter

In this study we observed significantly increased ONSD in patients with pituitary adenomas. The ONS is a layer of dura mater that surrounds the subarachnoid space and the optic nerve³³. Because the subarachnoid space is contiguous with the cerebrospinal fluid in central nervous system, elevated intracranial pressure (ICP) is transmitted to the subarachnoid space³³. Historically, distension of the ONS has been associated with cerebrovascular diseases and is considered a surrogate marker for elevated ICP^{15,33}. Raised ICP can also result from a focal intracranial mass, such as a tumor¹³. While the relationship between volume and pressure within the cranium is not linear, increasing intracranial contents raises ICP once compensatory mechanisms are depleted¹³. Globally elevated ICP may explain our finding of ONS distension in this study.

Alternatively, increased ONSD in patients with adenomas may also reflect TSD. Retrograde TSD (rTSD) is the process by which neuronal damage is promulgated “upstream”, or in the direction of the cell body¹⁹. rTSD has been reported in the form of retinal thinning following occipital damage¹⁸ and in retinal cell degeneration following insult to the LGN². Reduced thickness of the retinal nerve fiber layer has also been found in patients with chiasmal compression¹⁰, implicating rTSD in secondary pathology caused by suprasellar lesions. Axonal swelling, a hallmark of rTSD¹⁹, may be one mechanism by which the ONS distends in patients with pituitary adenomas.

While increased ONSD is typically attributed to elevated intracranial pressure¹⁵, this is the first study that quantifies changes in ONSD in adenoma patients. More work is required to determine whether these changes are a result of rTSD, globally increased intracranial pressure, or another pathological substrate.

Limitations

The primary limitation of this study is the small sample size, which may have prevented some of our analyses from achieving statistical significance. Additionally, not all patients in this study underwent neuro-ophthalmological examination. Indeed, some analyses yielded *p*-values that approached significance but did not withstand correction for multiple comparisons, factors that may be attributable to small sample size. While 7T MRI has the offers enhanced contrast and higher resolution over standard clinical MRI, the eligibility criteria for 7T imaging are more stringent than those used at lower field strengths, making patient enrollment logistically challenging.

While high spatial resolution dMRI enabled accurate reconstruction of the optic tracts and radiations, diffusion characteristics of the optic nerves were not obtained. We were unable to achieve adequate dMRI signal anterior to the optic chiasm due to gradients in the local magnetic field caused by the shift in magnetic susceptibilities between tissue and air near the sphenoid sinus. Instead, the high-resolution T₂-TSE used to measure structural changes anterior to the chiasm was considerably more resistant to artifact. Advanced shimming techniques with insert shim gradients are future developments that may help to reduce B0 inhomogeneity artifacts in this region.

While quantitative imaging metrics collected in this study are valuable for determining the impact of suprasellar lesions on visual pathway structures, post-operative imaging would be useful to characterize structural and microstructural changes following surgical decompression of the optic chiasm. Follow-up imaging to identify imaging markers of recoverability within the visual pathways is an area of future investigation in our group.

Lastly, because of the complex anatomy of the optic radiations, tractography parameters used to reconstruct these fibers are not standardized⁵. The parameters we employed were chosen with the objective of including as many “true” fibers as possible, especially with regard to the sharp turn at Meyer’s Loop. Qualitative comparison of our tractography to known anatomy showed good agreement, however, validation of tractography using *ex vivo* samples will be important for establishing a ground truth and optimizing algorithm parameters to precisely identify the optic radiations *in vivo*.

5. Conclusions

To our knowledge, this is the first study to employ T dMRI to probe the visual pathway in patients with pituitary adenomas. We believe that the high spatial resolution afforded by ultra-high field MRI permits excellent reconstruction of the visual pathway. These findings suggest contributions of both aTSD, evidenced by disordered diffusion indices of optic tracts and radiations as well as reduced cortical thickness in V1, and rTSD in the form of increased ONSD. We also found strong correlations between quantitative imaging of the visual pathways and results from neuro-ophthalmological examination, suggesting that advanced imaging techniques are capable of assessing the functional impact of suprasellar lesions on visual function.

Diffusion-weighted imaging of the visual pathways offers a promising method for determining secondary effects of chiasmal compression and identifying tumor-related degeneration in otherwise healthy-appearing structures. These findings may be useful in i) objective grading of existing damage to the visual pathway to determine indication for surgical decompression and ii) predicting the considerable variability in visual recovery post-surgery, serving as a pre-operative marker of vision recoverability for patients with pituitary adenomas.

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ABBREVIATIONS

aTSD	anterograde TSD
DWI	diffusion-weighted MRI
FA	fractional anisotropy
FDR	false discovery rate
LGN	lateral geniculate nucleus
MD	mean diffusivity
OCT	optical coherence tomography
PSD	pattern standard deviation
RNFL	retinal nerve fiber layer
ROI	region of interest
TSD	transsynaptic degeneration
T2-TSE	T2-weighted turbo spin echo
VFD	visual field defect
V1	primary visual cortex

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Figure 1.

Regions of interest used for probabilistic tractography. Panel A: Diagram of the human visual pathway. Panel B: Coronal T₂-TSE image of the optic chiasm (white arrowhead) in a healthy participant. Panel C: Coronal T₂-TSE image of a compressed optic chiasm (white arrowhead) in a patient with a pituitary adenoma. Panel D: Coronal quantitative T₁-map of the lateral geniculate nuclei (white arrowheads). Panel E: Sagittal T₁-weighted image with the FreeSurfer segmentations of the cuneus (blue) and pericalcarine (red) cortices.

Figure 2.

Schematic of the structural measurement acquired. Panel A: Axial T₂-TSE image with the left and right ONSD measured. Panel B: Coronal T₂-TSE with the pituitary adenoma measured. Panel C: FreeSurfer derived cortical thickness map. Panel D: Coronal T₂-TSE with the optic chiasm center deflection measurement in a patient with a pituitary adenoma. Panel E: Magnified left ONSD measurement.

Abbreviations: ONSD, optic nerve sheath diameter.

Figure 3. Probabilistic tractography of the optic tracts and radiation overlaid on quantitative T1-maps. Panels A-C: Reconstructed optic tracts in axial, coronal, and sagittal orientations. Panels D-F: Reconstructed optic radiations in axial, coronal, and sagittal orientations. Panel G: 3-dimensional rendering of probabilistic tractography of the optic tracts and radiations.

Figure 4.

Spatially normalized diffusion profiles of the optic tracts and radiations. The top row shows FA data and the bottom row contains MD data. Results are averaged across 16 patients and 16 matched controls. Pituitary adenoma patient data are shown in red, control data are shown in blue. Dashed lines represent 1 standard deviation above and below the mean. *Abbreviations:* FA, fractional anisotropy; LGN, lateral geniculate nucleus; MD, mean diffusivity.

Figure 5.

Pearson's correlational coefficients between tumor volume and diffusion indices of the optic tracts and radiation. Panel A: Correlation between tumor volume and FA of the optic tracts ($r = -0.50$, $*p = 0.044$). Panel B: Correlation between tumor volume and FA of the optic radiation ($r = -0.20$, $p = 0.43$). Panel C: Correlation between tumor volume and MD of the optic tracts ($r = 0.80$, $*p = 0.0002$). Panel D: Correlation between tumor volume and MD of the optic radiation ($r = 0.66$, $*p = 0.0061$).

Table 1.

Demographic and disease characteristics of participants.

	PA Patient (Entire Group)	PA Patient (Matched)	Control
Age, M (sd)	47.6 (12.1)	44.9 (9.8)	43.8 (9.9)
Male, n (%)	10 (55.6%)	8 (50%)	8 (50%)
Chiasm Thickness mm (sd)	1.44 (0.70)	1.43 (0.74)	2.3 (0.55)
Chiasm Deflection mm (sd)	2.54 (3.66)	2.58 (3.88)	−0.11 (0.31)
Tumor Volume mm ³ (sd)	7320.1 (9154.7)	8044.2 (9480.1)	--
Left Mean Deviation dB, n (sd)	−7.67, 9 (8.26)	--	--
Right Mean Deviation dB, n (dB)	−10.35, 9 (11.08)	--	--
Left PSD dB, n (sd)	5.83, 9 (3.97)	--	--
Right PSD dB, n (sd)	6.05, 9 (4.45)	--	--
Left RNFL μ m, n (sd)	78.71, 7 (17.66)	--	--
Right RNFL μ m, n (sd)	77.0, 7 (18.52)	--	--

Abbreviations: dB, decibels; PA, pituitary adenoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Table 2.

Pearson correlation coefficients and FDR-adjusted p -values between radiological findings and neuro-ophthalmological examination. p -values below the significance threshold are in bold face.

	RNFL (μm)	Mean Deviation (dB)	PSD (dB)
<i>Optic Tract</i>			
FA	0.60 (0.42)	0.81 (0.016)	-0.73 (0.05)
MD	-0.54 (0.42)	-0.88 (0.008)	0.87 (0.006)
<i>Optic Radiation</i>			
FA	-0.29 (0.70)	-0.21 (0.59)	-0.11 (0.78)
MD	-0.01 (0.71)	-0.53 (0.19)	0.69 (0.05)
Tumor Volume (mm^3)	-0.28 (0.55)	-0.70 (0.056)	0.89 (0.004)

Abbreviations: dB, decibels; FA, fractional anisotropy; MD, mean diffusivity; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Table 3.

Summary table of group difference results. Mean (standard deviation). MD values are $\times 10^{-4} \text{ mm}^2/\text{s}$. *p*-values below the Bonferonni-adjusted threshold are shown in bold face.

	Patient	Control	Effect Size (%)	<i>p</i> -value
Left Optic Tract				
FA	0.37 (0.07)	0.48 (0.05)	-22.9	< 0.001
MD	9.07 (1.19)	8.48 (0.86)	+6.96	> 0.05
Left Optic Radiation				
FA	0.50 (0.06)	0.60 (0.03)	-16.67	< 0.001
MD	7.25 (0.50)	6.82 (0.24)	+6.74	0.002
Right Optic Tract				
FA	0.38 (0.07)	0.48 (0.06)	-20.83	< 0.001
MD	9.14 (1.39)	8.72 (0.85)	+4.82	> 0.05
Right Optic Radiation				
FA	0.48 (0.06)	0.59 (0.02)	-18.64	< 0.001
MD	7.28 (0.58)	6.60 (0.21)	+10.30	< 0.001
Left ONSD (mm)	5.31 (0.79)	4.48 (0.60)	+18.53	0.009
Right ONSD (mm)	5.30 (0.79)	4.50 (0.61)	+17.78	0.01
Left V1 (mm)	1.60 (0.14)	1.71 (0.10)	-6.43	0.01
Right V1 (mm)	1.64 (0.10)	1.75 (0.11)	-6.29	0.004
Left Average Cortex (mm)	2.28 (0.13)	2.36 (0.08)	-3.39	> 0.05
Right Average Cortex (mm)	2.26 (0.14)	2.33 (0.07)	-3.00	> 0.05

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; ONSD, optic nerve sheath diameter; V1; primary visual cortex.