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A decade of DTI: what the advanced MRI technique of diffusion tensor imaging has taught us about the effects of cerebral gliomas on white matter tracts

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Plain Language Summary

Diffusion tensor imaging (DTI) is an advanced form of magnetic resonance imaging (MRI) that can image the white matter (axon) tracts in the brain by measuring the difference in water diffusion between normal cells and fluid within the brain (water diffuses equally in all directions and has a high **mean diffusivity**) and the highly parallel white matter tracts (water diffuses along tracts and not perpendicularly – axons have a high **fractional anisotropy**) (**Fig. 1*a,b***).

Until DTI, microscopic study of brain biopsies and post-mortem tissue was the only way to study axon tracts in the human brain. DTI mapping (**Fig. 1*c,d***) allows us to image these tracts and measure their integrity both in health, and in pathologies like cerebral gliomas (tumour of the glial cells within the brain). So what has DTI taught us about glioma effects on white matter tracts? Early gliomas cause deflection (but not damage) to axon tracts due to their mass and the fixed volume of the brain (**Fig. 2*b***). They also irritate the surrounding tissues causing inflammation and oedema (fluid release), which slows down nerve transmission but again, does not damage axon integrity (**Fig. 3*b***). More advanced gliomas invade along the parallel axon tracts, causing further change in orientation and damage to neuronal transmission (**Fig. 4*b***). Finally, late-stage tumours cause complete destruction of the tracts, with DT images of this stage indicating a high mean diffusivity (destroyed tracts resemble disordered cells/fluid rather than intact axon tracts).

DTI has taught us a great deal about glioma pathology but further study is needed before we can use this information to improve surgical removal of gliomas and reduce postoperative disability.

Overview

Cerebral glioma pathology often causes a reduction in neuronal transmission in adjacent white matter tracts (WMTs)[1]. Diffusion tensor imaging (DTI) is an advanced MRI technique that utilises the highly parallel structure of WMTs to image axon transmission and direction (**Fig. 1**). This technique allows detailed mapping of brain processing and extrapolation of fractional anisotropy (FA) and mean diffusivity (MD). FA shows degree of anisotropic diffusion (**linear diffusivity**), and MD indicates the degree of isotropic diffusion occurring in an axon tract (**diffuse diffusivity**).

Glioma resection has a high degree of recurrence and disability post-surgery[3]. This critical analysis of DTI literature from the past 10 years elucidates four 'stages' of glioma effects on WMTs[4], and concludes that FA and MD changes in peritumoural axon tracts elucidate a pattern that might allow identification of normal, infiltrated and glioma tissue. This would guide surgical resection by minimising postoperative defects, reducing tumour recurrence, and assessing prognosis following surgery.

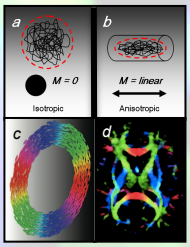

Figure 1[2]. Isotropic diffusion ***a***; and anisotropic diffusion; ***b***. **c;** illustrative diagram and **d;** diffusion tensor map, both colour-coded for tract direction.

Findings

Stage One: Tumour Bulk Mass Effect

Pre-infiltrative gliomas commonly distort WMTs by means of their physical mass within the fixed volume of the skull[5]. An early DTI study showed deviation in symmetry of WMTs by 30º without any loss of axonal transmission[6]. This manifests as a colour change in the DTI image with no loss of tract intensity (**Fig. 2**).

Despite no obvious loss of functionality from this 'bulk mass' effect, deviated WMTs show a subtle FA reduction in axons within the lesion[8], and an increase in FA in extralesional axon tracts[9]. If this relationship could be proven within a single, large-scale trial, this is a pattern that might allow identification of fibres under immediate risk from tumour expansion in glioma patients.

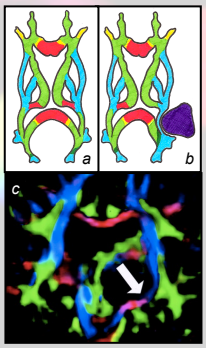

Figure 2[7]. ***a*** shows normal axon tract colour-coded for orientation; glioma causes mass deflection shown as colour change, in diagram ***b***; and DTI image, ***c***.

Stage Two: Peritumoural oedema

Oedema is commonly induced near glioma pathology and favours isotropic (diffuse) diffusion, increasing MD and reducing FA in axon fibres[10]. Axonal transmission is reduced but destroyed, and the DTI pattern shows normal tract orientation with reduced colour intensity (loss of linear diffusion) (**Fig. 3**).

Resection of such fibres would lead to a postoperative deficit and if not infiltrated, fibres should avoided in surgery. Manipulation of the threshold at which tracts have high enough linear diffusion (FA) to show up as WMTs on DT images allows identification of tracts with reduced FA, including oedematous tracts. This allows us to distinguish normal from oedematous WMTs, which could be used both pre- and intraoperatively to avoid resection of intact oedematous axons.

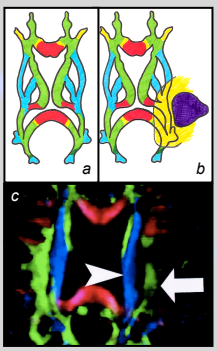

Figure 3[7]. ***a*** shows normal axon tract colour-coded for orientation etc; peritumoural oedema has little effect on axon trajectory (no colour change) but reduced anisotropy shown as reduced colour intensity in ***b*** and ***c***.

Stage Three: Infiltration along axon tracts

Glioma invasion occurs preferentially along WMTs and cause axon deflection, oedema and drastically reduced FA not accounted for by bulk mass effect alone (**Fig. 3*a,b***). DT images (**Fig. 3*c***) show both loss of anisotropy (reduced colour intensity) and change in axon orientation (colour change from blue to green at arrowhead) and have been confirmed to indicate tumour invasion by histological studies[11]. Of these infiltrated axon fibres, as many as 24.5% show active white matter tissue within the lesion advancing border[12]. This further guides glioma management by identifying that one quarter of surgical procedures may lead to a postoperative deficit in advancing border resection. Use of DTI in preoperative gliomas would thus introduce difficulties in deciding whether to resect a tumour border that would cause a definite postoperative deficit, but would also improve the choice available to physicians and patients in glioma.

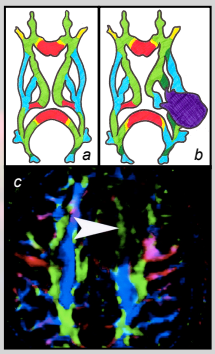

Figure 4[7]. ***a*** shows normal axon tract colour-coded for orientation; glioma invasion of tract causes change in axon orientation (colour change in ***b,c***) and loss of FA (colour intensity) in ***c***.

Stage Four: Ischaemia and neuronal degradation

The advanced stages of glioma pathology show widespread ischaemia, Wallerian degeneration and extensive neuronal death (**Fig. 3*b***). Peritumoural WMTs are destroyed, FA falls to zero and MD shows isotropic (equal in all directions) diffusion[5]. Studies manipulating the FA threshold to almost zero show no intact pathways running through the lesion, but fail to measure satisfactorily whether complete tract degeneration has occurred[13]. It is likely that no neuronal transmission occurs in tracts below a certain FA threshold, and future large studies might allow calculation of a definite or proportional FA value at which tracts can be safely resected with minimal postoperative deficit. This would be of the utmost use in low grade gliomas, which could be resected over several sessions, allowing iatrogenic effects to be minimised.

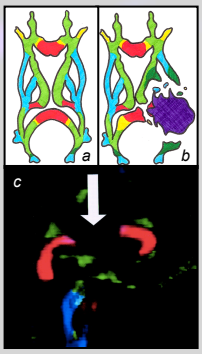

Figure 5[7]. ***a*** shows normal axon tract colour-coded for orientation; neuronal degradation manifests with an FA as low as zero and a MD equal to free-flowing fluid (CSF) within the brain (tract indistinguishable from background in ***b*** and ***c***).

Conclusions & Future Work

Future investigations are required to improve on the results from current studies, many performed on a small scale with low reproducibility. Difficulty in reproducibility is due to the lack of DTI standardisation, an area that has seen several key innovations[14,15], but remains to be perfected and rigorously applied to glioma imaging. DTI has helped expand our knowledge of WMTs in cerebral glioma and may one day be used to guide surgical resection, but this promise remains to be fully realised in the studies appraised.

It is hoped that the next ten years will see the development of functional DTI standardisation that will allow consistently automated selection of brain tissue into regions of glioma, transition and normal tissue with high reproducibility. This would one day allow the development of a DTI algorithm, usable pre- and intraoperatively, that could consistently and accurately identify functional tissue within glioma resection boundaries, allowing maximisation of tumour resection whilst reducing postoperative functional defects. Additionally, manipulation of the FA ratio would allow oedematous and infiltrated axon tracts to be identified in order to guide surgical resection and increase the preoperative choices available to glioma patients. This would improve on current techniques by taking into account intraoperative tissue shift, and would provide an advantage over fMRI (which indirectly depicts sites of WMT activation through changes in regional blood flow) by depicting integral axon characteristics such as fibre density and myelination.

References

[1]Price SJ *et al.* (2003) Diffusion tensor imaging of brain tumours at 3 T: a potential tool for assessing white matter tract invasion? Clin Radiol 58:455-462.

[2]Figure 1: Overview of iso- and anisotropic diffusion and use in DTI to show axon tract orientation. Sections ***a*** and ***b*** original, ***c*** and ***d*** adapted from: Jellison BJ *et al.* (2004) Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. Am J Neuroradiol 25:356-369.

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[7]**Figure s 2-5**. Sections ***a*** and ***b*** original, ***c*** adapted from Jellison *et al.*, 2004[2].

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