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Review article

Prevention of radiotherapy-induced neurocognitive dysfunction in survivors of paediatric brain tumours - the potential role of modern imaging and radiotherapy techniques

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Brief title: Prevention of neuro-cognitive dysfunction in brain tumours

Abstract

Neurocognitive dysfunction is the leading cause of reduced quality of life in the long-term survivors of paediatric brain tumours. Radiotherapy is one of the significant contributors to neuro-cognitive sequelae. The current approaches in prevention and/or reduction in neurocognitive dysfunction include avoidance of radiotherapy in young children and reduction of radiotherapy dose and volume of brain irradiated. There have been considerable advances in brain imaging, especially with functional imaging and fibre tracking using diffusion tensor imaging. Radiotherapy techniques for photon therapy have also evolved in recent years with the wide-spread use of techniques such as image-guided radiotherapy (IGRT), volumetric modulated arc therapy (VMAT), helical tomotherapy, and adaptive radiotherapy (ART). The number of proton beam therapy facilities is increasing globally and there is a great enthusiasm for the clinical use of newly developing MRI-guided radiotherapy systems. We review the potential role of modern imaging and innovative radiotherapy techniques in minimising neurocognitive sequelae in children with brain tumours and various strategies to integrate these advances to drive further research.

Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms "brain tumours", "radiotherapy", "imaging", "functional mapping", "diffuse tensor imaging", "fibre tracking", "intensity-modulated", "proton beam", "MRI-Linac", "IGRT", "VMAT", "Tomotherapy" from 1990 to June 2016. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Introduction

Brain tumours, the most common solid tumours in children, constitute more than 20% of paediatric cancers (1, 2). With the current advances in treatment, more than 70% of children are long-term survivors (3). Almost a half of paediatric patients will develop progressive neurological deficits (4). This is reflected in lack of attainment of academic and professional potential (5).

The development of neurocognitive dysfunction is contributed to by a number of disease-, treatment- and host-related factors such as location and size of the tumour, age at diagnosis, surgery, radiotherapy, chemotherapy, and premorbid intellectual and neurological function (6). Studies also suggest that genetic effects may influence various elements of cognitive function (7).

Radiotherapy is one of the major contributing factors to neuro-cognitive dysfunction, which is typically progressive in nature (5, 8). Cognitive dysfunction can affect four main domains: global cognitive functioning (IQ), academic achievements, executive function, and psychomotor skills (6, 9). Prevention or minimization of radiation-induced cognitive dysfunction has been a topic of intense research for a long time. The only measures which have achieved some success to date are avoidance of radiotherapy in young children, especially less than three years of age and reduction in the total radiation dose and volume of brain irradiated (10, 11).

Recently, there have been considerable advances in brain imaging, particularly with functional mapping and fibre tracking using diffusion tensor imaging (12). Some of these advances are being exploited in the surgical management of brain tumours and radiosurgery (13-16). However, integration of these technologies to improve radiotherapy planning is slow. In this article, we review the role of modern imaging in understanding neurocognitive dysfunction, discuss the potential role for imaging and innovative radiotherapy techniques in minimising neurocognitive sequelae, and derive inspirational strategies to integrate these advances to drive further research.

Mechanisms of radiation-induced neurocognitive dysfunction

Radiotherapy can damage progenitor cells, inflammatory and stromal cells, and vasculature (17). Radiotherapy induced inflammation, angiogenesis and cell death can lead to white and grey matter damage (9). Both white and grey matter development depends on the age of the individual and full myelination of the cerebral cortex is achieved only in early adulthood. In adults, neurocognitive dysfunctions are irreversible and progressive, affecting particularly the domains of processing speed and memory and in severe cases leading to ataxia, urinary incontinence, and dementia in 2-5% (18, 19). In children, radiotherapy can prevent age-appropriate normal maturation and myelination of brain and/or damage to white matter tracts (20). The molecular effects of radiotherapy-induced cognitive dysfunction have been reviewed recently (21).

Impact of radiotherapy parameters

The risk and severity of neurocognitive dysfunction depends on a number of patient-and disease-related factors and radiotherapy parameters. Studies show that the risk of neurocognitive dysfunction increases with increasing dose of radiotherapy, with a progressive deterioration over time (22, 23). Radiotherapy prevents children acquiring new skills and knowledge, leading to progressive worsening of deficit over time (5). In a meta-analysis, cranial radiotherapy, chemotherapy and longer time since diagnosis were associated with lower general intelligence (24). Children with infratentorial tumours and younger age have a higher risk of neurocognitive dysfunction (8, 25). Children under 3 years are particularly vulnerable to deleterious effects of radiotherapy due to rapid cell proliferation and myelination and dendritic and axonal outgrowth and radiotherapy is generally avoided in this age group (10, 24).

Eloquent brain areas and domains in neuro-cognition

A number of areas are important in neuro-cognition, but the relative contribution of individual areas in overall cognition is still to be fully understood. Neurons and glial cell are produced from the neurogenic stem cells located in the subventricular zone of the lateral ventricles and subgranular zone of the hippocampal gyrus (26). These areas are part of the limbic system and continuous renewal of neurons from the stem cells is important in memory (27). The limbic system consists of hippocampus, parahippocampal gyrus, and amygdaloid. These structures located in the temporal lobe are important in various aspects of memory and emotional learning. In a study of 32 children treated with proton therapy, even though neurocognitive function is relatively spared, children less than 7 years and those who received a higher dose to the left temporal lobe or hippocampus had worse neuro-cognitive dysfunction (28).

The frontal pole, anterior cingulate and frontal white matter horn are important in working memory and executive function, whereas the corpus callosum is involved in cognition and processing speed (29, 30). The stem cells within the subventricular zone (SVZ) are important in injury repair and thereby maintain the ability for life-time learning (31, 32). The hippocampus which forms part of the limbic system is involved in the consolidation of new memory (33-35). While the impact of radiation to these areas is not correlated with neurocognitive dysfunction in prospective studies, a number of studies in adults with brain metastases have shown that with sparing of the hippocampi, the incidence of neuro-cognitive sequelae can be significantly reduced (36). However, the role of hippocampal sparing to preserve cognitive function in children is yet to be studied and it is not certain that a simple sparing of the hippocampus, which measures approximately 1% of total brain volume, would be sufficient to prevent neurocognitive dysfunction in children (32). It is also unknown whether sparing of a unilateral hippocampus has an impact on preservation of cognition. Studies of metastatic brain tumours in adults suggest that the risk of recurrence in the hippocampal region is low and therefore hippocampal sparing is a feasible option without

compromising local control of disease (37, 38). However, neither the true incidence of hippocampal spread nor the risk of disease recurrence in the hippocampal region in paediatric brain tumours is known.

The neurons from the cerebellum form a series of closed loops with neurons in the prefrontal cortex, temporal lobes and limbic structures. Damage to these neurons could lead to the postoperative sequelae of posterior fossa syndrome (cerebellar mutism) in medulloblastoma and also to late neurocognitive dysfunction (39, 40).

Conventional imaging in neurocognitive dysfunction

Conventional anatomical MRI changes include white matter changes, mild enhancement, and oedema in the distribution of the radiation field (17). Diffuse white matter changes (often referred to as leucoencephalopathy) develop in 16% of children treated with radiotherapy for malignant brain tumours after a median interval of 7.8 months (41). These lesions were most commonly seen in the pons and cerebellum and 73% of lesions fully resolved after a median interval of 6.2 months (41). In children with acute lymphoblastic leukaemia (ALL) who were only treated with chemotherapy, white matter changes were found in 10% at the end of treatment and in 12% of patients at 5 years (42). Although a minority of patient with these white matter lesions develop permanent neurological deficits, the development of these lesions appears to be a poor predictor of neurocognitive deficits (41-43).

It is recognised that volumetric measurement of the brain can identify global atrophy and that chemoradiotherapy in adults with brain tumours results in loss of brain volume (44). Studies correlating global brain volume changes have failed to show any association in adult survivors of paediatric brain tumours (45).

It is clear that conventional MR methods are not sensitive enough to identify changes that predict neurocognitive dysfunction. The development of new imaging methods sensitive to pathological alteration will allow better understanding of these changes.

Importance of white matter structures on neurocognitive decline

Studies that measure changes in white matter volume have shown that decrease in white matter volume following radiotherapy correlates with IQ decline and neurocognitive decline (46-49). Voxel based morphometry approaches show that frontal white matter (especially right sided) is more sensitive to volume loss than other parts of the brain (48). Increased white matter volume loss is associated with intensity of CNS treatment (i.e. treatment for brain tumours has a greater effect than craniospinal irradiation for ALL), younger age of treatment and the interval between treatment and imaging study (50).

Advanced MRI techniques for brain imaging

Functional MRI using BOLD imaging

Functional MRI (fMRI) is a well-established technique to identify cortical areas that are activated undertaking a specific task. During cortical activation there is a transient, focal increase in blood flow that can be measured by differences in the magnetic properties of haemoglobin depending on its oxygenation status. Deoxyhaemoglobin is paramagnetic and as a result shortens the T2* of the blood and its surroundings. Oxyhaemoglobin is diamagnetic, and as a result increasing oxygenation of blood reduces the T2* shortening and increases the T2* signal. This 'blood-oxygen-level dependent' (BOLD) contrast can be detected using heavily T2*-weighted sequences such as gradient-recalled echo (GRE) and echo planar imaging (EPI). The transient increase in T2* signal during activation is small and detected by statistical analysis. BOLD signal intensity is reduced with increasing age, increasing tumour grade, proximity to tumour, and previous surgery (51-55). The accuracy of the BOLD imaging in detecting areas of activation has been assessed in adults undergoing awake surgery with cortical stimulation. There appears to be very good accuracy of fMRI correctly identifying regions of motor activation as compared to the gold standard of direct cortical stimulation (sensitivity of 87% and specificity of 88%) (56). This accuracy decreases with increasing tumour grade (56). Overall the discrepancy between fMRI and cortical areas stimulated were only 6 – 13.8 mm (57). All studies suggest 96-100% of fMRI activated areas were within 2 cm of cortical stimulation: the difference may be due to registration errors (57). There is reasonable repeatability of motor function.

Language function, however, is not so well localized by BOLD imaging. Studies correlating fMRI activation with cortical stimulation show that sensitivity and specificity are worse than motor (80% and 78% respectively) (56). As BOLD signal can be affected by proximity to the tumour, even lateralising language function can be affected by the reduced volume of BOLD effect if it is near the tumour and so can be misleading (58). It is clear that use of multiple language tasks improves accuracy. The sensitivity of naming or verb generation on their own is 22% and 36% respectively. This improves to 59% if these tasks are combined (59). The repeatability of detecting language function is very poor – for individual tasks the overlap is 9-26%. This improves to 39-44% if they are combined (60). Test-retest accuracy was worse in high-grade tumours compared to low-grade (61).

Resting State fMRI

The fMRI methods described above are all task based where changes in blood flow are measured during a task and compared to rest. This accounts for a fraction of the brain activity and it was realized that BOLD fluctuations can be identified at rest. By correlating these regions of BOLD activation it is possible to link regions and develop networks. The methodology and background to this technique of resting state fMRI has recently been reviewed (62). There is much interest among cognitive neuroscientists to use this to study brain networks and metrics of this network has been shown to correlate with cognitive

reserve (63). This has not been used to assess impact of radiotherapy but is an exciting method for future research.

Diffusion tensor imaging of white matter integrity

Diffusion tensor imaging (DTI) helps to study the integrity of white matter structures. DTI, in which uses a magnetic resonance signal visualizes water movement within axons, has been used to study white matter development in children. Diffusion of water is high along, and low perpendicular to white matter tracts, resulting in an anisotropic diffusion profile. If you could plot the location of a water molecule diffusing through the brain it would be in the shape of an ellipse with the long axis describing the principal axis of diffusion. Tensor calculus can be used to provide quantification of this tensor. The commonest method of quantifying anisotropy uses the fractional anisotropy (FA) value which lies between 0 (for isotropic diffusion, i.e. diffusion is equal in all directions) and 1 (maximum anisotropic diffusion, i.e. along one axis). The degree of anisotropy depends on white matter fibre diameter and density, the myelin sheath, other macromolecular structure that hinder proton diffusion and fibre-tract coherence (64). By linking adjacent 'ellipses' in different voxels using the principal axis it is possible to develop a probabilistic map of white matter tracts (tractography). DTI tractography is useful for characterising the major white matter pathways (65).

Studies have shown that development in cognitive function in children and adolescents correlates with an increase of FA (66, 67). Studies looking at the effect of radiotherapy on white matter tract integrity have shown a reduction in FA in white matter of children treated with radiotherapy and this decrease in FA correlates with IQ, tests of neuropsychology function, and school performance (45, 49, 68-71). The decrease in FA is more noticeable with earlier age radiotherapy and increased radiotherapy dose (68, 70-73). The interval between radiotherapy and the DTI study provides differing results, with some studies suggesting it is correlated with reduced FA whilst others found no association (70, 71).

What is clear is that some regions of the brain are more sensitive to radiotherapy than others. Studies have shown a greater decrease in FA in the frontal and temporal lobes (74-76). This reduction, especially in the frontal lobes, is greater despite similar doses of radiotherapy (68). Reduction in FA in frontal and parietal lobes is associated with neurocognitive decline (77). Other structures that are affected by radiotherapy include periventricular white matter, corpus callosum, anterior and posterior limbs of the internal capsule, the corona radiata, and fornix (69, 75, 78, 79).

The difficulty with using DTI to study changes in white matter integrity from radiotherapy is that chemotherapy alone can lead to white matter disruption. Studies in patients treated with chemotherapy alone had reduced FA in white matter. Reduction in FA in the corpus callosum was associated with neurocognitive decline, and a reduction in FA in the inferior fronto-occipital fasciculus was associated with a diminished motor processing speed (20). Comparing patient groups that received chemotherapy with radiotherapy showed a larger reduction in FA compared with patients treated with chemotherapy alone (70, 80).

Another problem is that changes in FA do not appear to be diagnostic. There are other studies in children reporting a lower FA in several eloquent brain regions, but without any correlating specific neurocognitive dysfunction (69) (table 1).

Advanced radiotherapy techniques

There are no prospective studies evaluating the role of selecting sparing of various eloquent areas and domains of brain associated with different elements of cognitive function. A retrospective, which has evaluated radiotherapy dose to potential functional targets of cognitive function, has shown that radiotherapy to the corpus callosum, left frontal white matter, right temporal lobe, bilateral hippocampi, subventricular zone and cerebellum affected global cognitive outcome at doses <60 Gy (32).

While, the dose threshold of these different structures for cognitive decline is unknown, the modern radiotherapy technology can effectively spare or minimise radiotherapy to any brain structures. For example, advanced intensity-modulated radiotherapy (IMRT) methods such as volumetric modulated arc therapy (VMAT) and helical tomotherapy are used effectively to spare hippocampi in brain tumours (36, 81-83).

The physical advantage of proton therapy in terms of a significant reduction in radiotherapy dose to normal tissues outside the tumour volume could be exploited to reduce the neurocognitive dysfunction following radiotherapy (84). In a study of children with low-grade glioma treated with proton therapy ($n=32$), 12 had neurocognitive assessment, which did not show any significant declines in Full-Scale Intelligence quotient (FSIQ) at a median of 4.5 years (28). However, dose to the left temporal lobe/hippocampus was associated with decline in cognitive function. In a recent phase II study of proton therapy for medulloblastoma, there was a decline in FSIQ of 1.5 points per year (95% CI 0.9-2.1) primary due to a decline in processing speed and verbal comprehension (85). However, perception reasoning and working memory were not affected at a median follow-up of 5.2 years. FSIQ declined significantly in children <8 years.

While the initial reports of modern radiotherapy techniques and proton therapy are encouraging, none of the studies correlated the radiotherapy dose to different eloquent areas or domains with neurocognitive function.

The potential for integrating modern imaging with novel radiotherapy technique

Strategies to prevent or minimise radiation-induced neurocognitive dysfunction include avoidance of radiotherapy in children less than 3 years, optimal integration with chemotherapy to minimise the total dose of radiotherapy and/or volume of brain treated, optimal target delineation using better imaging, and use of highly conformal radiotherapy techniques.

Modern radiotherapy planning is based on a conventional MRI scan co-registered with a planning CT scan. The clinical benefit of integration of functional imaging and tractography

for fractionated radiotherapy planning in brain tumour has not been studied. However, a number of studies have evaluated the role of functional imaging for radiosurgery treatment planning for benign brain conditions, particularly arteriovenous malformations (AVMs) (15, 16, 86, 87). The frequency of motor complications after corticospinal tractography-integrated-radiosurgery for patients with AVMs involving the basal ganglia and thalamus (n=24) were significantly less compared with a historical cohort (n=28) without tractography integration (4.2% vs. 17.9% p=0.021) (88). There was no significant difference in 4-year AVM obliteration rate (69% vs. 76%, p=0.68). In another study of 71 patients undergoing tractography integrated radiosurgery for AVMs (45 pyramidal tract, 22 optic radiation, and 13 arcuate fasciculus) with a median follow-up of 23 months, only one patient had new persistent morbidity from worsening of pre-existing dysaesthesia (15). Tractography is increasingly being integrated into radiosurgery planning for benign brain conditions (Figure 1).

In a feasibility study of 4 patients with low-grade glioma, Kovacs et al co-registered fMRI following acoustic, visual, somatosensory and numeral stimuli to a planning CT scan (89). The study showed that with fMRI based 3D conformal planning, radiotherapy dose to the superior and inferior temporal gyrus and lingual gyrus could be reduced by an average of 50%. A subsequent study of 10 patients with brain tumours confirmed the role of fMRI in reducing dose to critical organs without compromising tumour target coverage (90).

A planning study has shown that integrating diffusion tensor tractography into IMRT planning has significantly reduced radiotherapy dose to the corticospinal tract in patients with glioblastoma (91). In another study of 20 patients with high-grade glioma, bilateral motor cortex and corticospinal tracts were marked using integrated DTI and BOLD-fMRI as organs at risk (OARs), which led to a reduction in the dose of radiotherapy using IMRT (92). Thus studies have shown that both DTI and BOLD-fMRI can be integrated into planning CT/MRI scan to delineate critical nerve tracks and eloquent regions for functional avoidance radiotherapy (figure 2).

Challenges of integration of functional imaging for radiotherapy planning

There are no long-term longitudinal studies correlating radiotherapy tolerance of various brain domains with neurocognitive dysfunction. One of the pre-requisites for use of functional avoidance radiotherapy is the robust understanding of the patterns of spread of individual brain tumours and the potential risk of relapse in an eloquent track or part of the brain. This necessitates carefully planned patterns of relapse studies which should be correlated with individual functional MRI scans.

While planning of radiotherapy using fMRI seems to be feasible, it is not certain whether the treatment can be delivered daily with high accuracy. Adaptive radiotherapy techniques using image guidance are evolving for a number of cancers. However, this technology has not been fully evaluated in brain tumours. While routine radiotherapy planning involves co-registrations of MRI scan with CT scan, the usual treatment verification is mainly based on

bony anatomy. A robust method of delivery of functional avoidance radiotherapy using fMRI needs treatment verification with an MRI scan. MRI-LINAC is a new advance which integrates a verification MRI scan with the radiotherapy treatment machine to deliver MRI-guided adaptive radiotherapy (93). This technology could be exploited further to deliver MRI guided, functional avoidance radiotherapy for paediatric brain tumours in the future.

Future directions

Radiotherapy techniques are now able to avoid potential areas of neurocognitive function when combined with optimal imaging. This needs to be assessed prospectively with neurocognitive function and tumour control as the primary outcomes. However, without proper knowledge of patterns of failure of different brain tumours, it would be unsafe to avoid radiotherapy to areas of brain which may harbour tumour.

With prospective studies we would be able to identify eloquent areas and tracts important in cognition and to correlate the effect of dose and volume of radiotherapy on specific cognitive domains. These studies would pave the way to functional image-guided risk-adapted radiotherapy for children with brain tumours.

While the concept of integration of functional imaging and tractography with modern radiotherapy to identify knowledge gaps in the correlation of radiotherapy parameters and neuro-cognitive function appears to be attractive in principle, there are a number of logistic challenges which can be addressed only with a prospective multi-stage collaborative approach (figure 3). Unfortunately, this approach will not yield a quick result, which can be integrated into the routine clinical practice. Nevertheless, clinicians should not be discouraged to embark on a path of slow and steady but incremental progress towards developing functional-image guided avoidance radiotherapy in children with brain tumour to maintain the highest quality of life without compromising the chances of cure.

Table 1 Studies on the role of DTI in assessing neurocognitive dysfunction in children with brain tumours

Study	No of patients	DTI finding	Summary of conclusion
Malbott et al 2006(69)	8 medulloblastoma patients and controls	Reduced IQ is associated with increased ADC and reduced FA. Corpus callosum and anterior and posterior limb of internal capsule has most reduced FA.	Reduced FA and increased ADC seen mostly in anatomical regions and correlates with reduced IQ.
Khong et al 2006(68)	9 medulloblastoma patients (treated with RT and chemo) vs controls.	Reduced FA in all regions – even where conventional imaging normal. Greater decrease in FA correlated with earlier age of treatment, longer interval from treatment and reduced school performance	Treatment related reduced FA. Correlates with school outcomes. Age of treatment important factor.
Qiu et al 2007 (74)	22 medulloblastoma survivors and controls	Calculated difference of FA and calculated dose. Decreased FA has dose response. Reduced FA frontal WM more than parietal WM despite similar RT dose.	Reduced FA has dose and anatomical location relationship.
Aukema et al 2009(20)	17 patients treated for medulloblastoma or ALL all treated with chemotherapy	Reduced FA compared to controls. Correlates with neurocognitive decline from splenium and body of corpus callosum. Correlates with motor processing with inferior fronto-occipital fasciculus.	Reduced FA in treated patients. Regional variation leads to differences in functional deficit.
Rueckriegel et al 2010(75)	13 patients with pilocytic astrocytomas (not treated with RT) and 17 medulloblastomas (treated with RT)	Decreased FA in medulloblastoma in midline cerebellar structures, frontal white matter and body of CC – the latter two not seen in pilocytic astrocytoma.	Difference between group was RT. Significant difference in FA. No correlation with outcome.
Brinkman et al 2012(45)	20 patients with medulloblastoma	RAD (radial diffusivity) in the frontal lobes was negatively correlated with shifting attention and cognitive flexibility and FA in parietal lobe was positively correlated with working memory and	Reduced white matter integrity in multiple brain regions correlated with deterioration in executive function
Palmer et al 2012(94)	40 patients with medulloblastoma treated with	Patients had significantly lower FA throughout WM fibre tract compared to controls. Lower	Commissural fibres in the corpus callosum are negatively affected by disease and treatment

	surgery and radiotherapy compared with healthy controls	FA within genu, body and splenium of the corpus callosum is associated with lower processing speed	which leads to detrimental effects in cognitive processing.
Horska 2014(95)	8 brain tumours and 1 ALL, 9 normal developing children as control	Patients had 24% higher overall mean ADC in the hippocampus compared with control	Difference in tissue sensitivity to injury among gray matter regions may exist.
King 2015(96)	27 patients (14 had radiotherapy) compared with 27 healthy volunteers	Lower FA in the white matter of the anterior portion of corpus callosum, right middle temporal and frontal regions in the radiotherapy group and it correlated with intellectual performance	Lower white matter integrity leads to lower intellectual outcome. Radiotherapy and chemotherapy may contribute to white matter disruption
Rueckriegel 2015(49)	18 medulloblastomas vs. 15 pilocytic astrocytomas.	Changes in volume of WM: GM+CSF and reduction of FA correlate with cognitive function, IQ, processing speed and shifting speed.	Changes in FA and white matter volume loss correlates with neuropsychology outcomes.

Figure 1 Examples of integration of tractography with radiosurgery for benign brain conditions: (A) trigeminal neuralgia and (B) thalamotomy for tremor (Courtesy of Prof T Kaprealian, UCLA Department of Radiation Oncology, Los Angeles, USA)

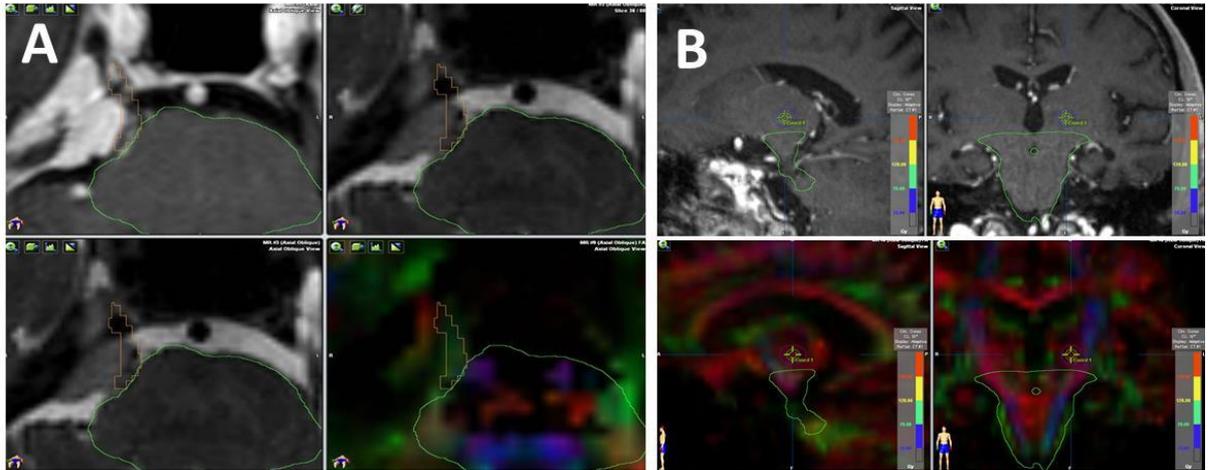


Figure 2 Functional BOLD MRI and tractography can be combined with anatomical MRI scan for treatment planning: (A) BOLD image after functional activation, (B&C) position of tract in relation to tumour and the brainstem and (D) volumetric representation of tumour (pink), activation areas (green), and tracts (yellow) superimposed on the brain surface (reproduced with permission from BRAINLAB)

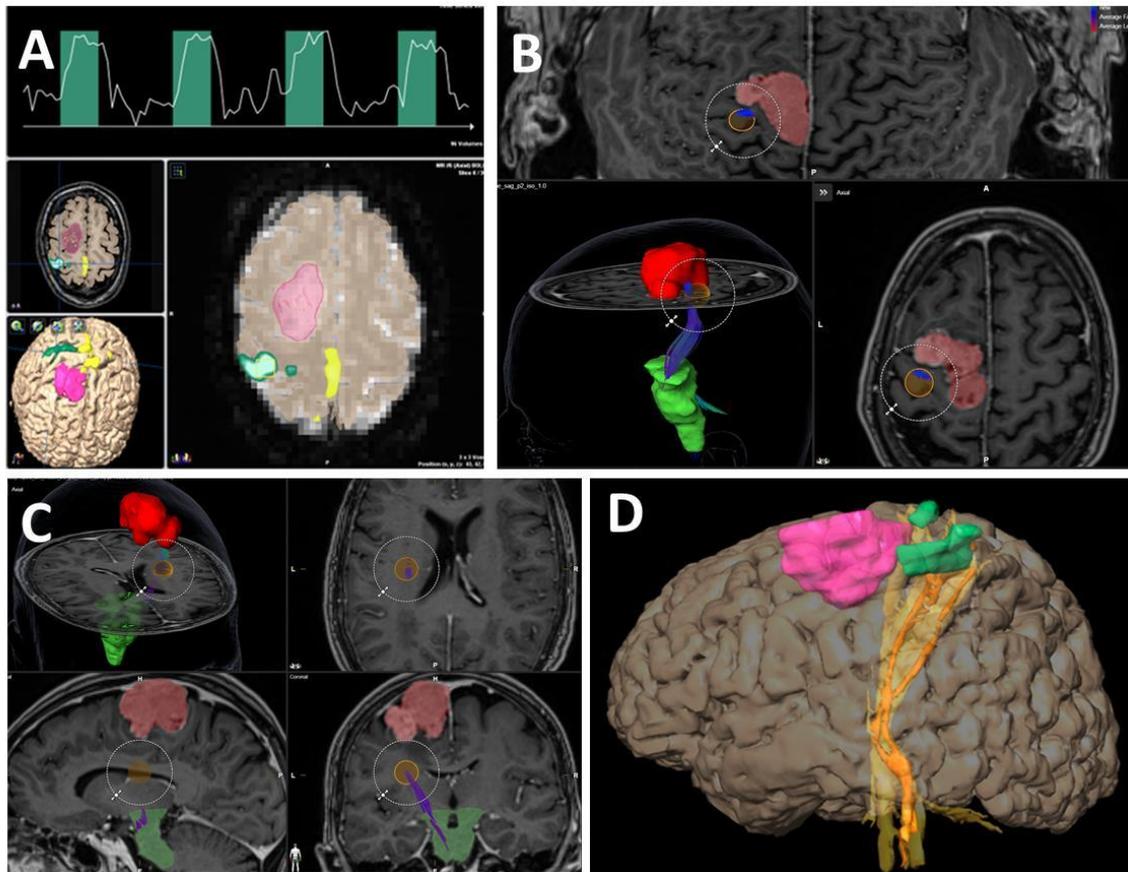
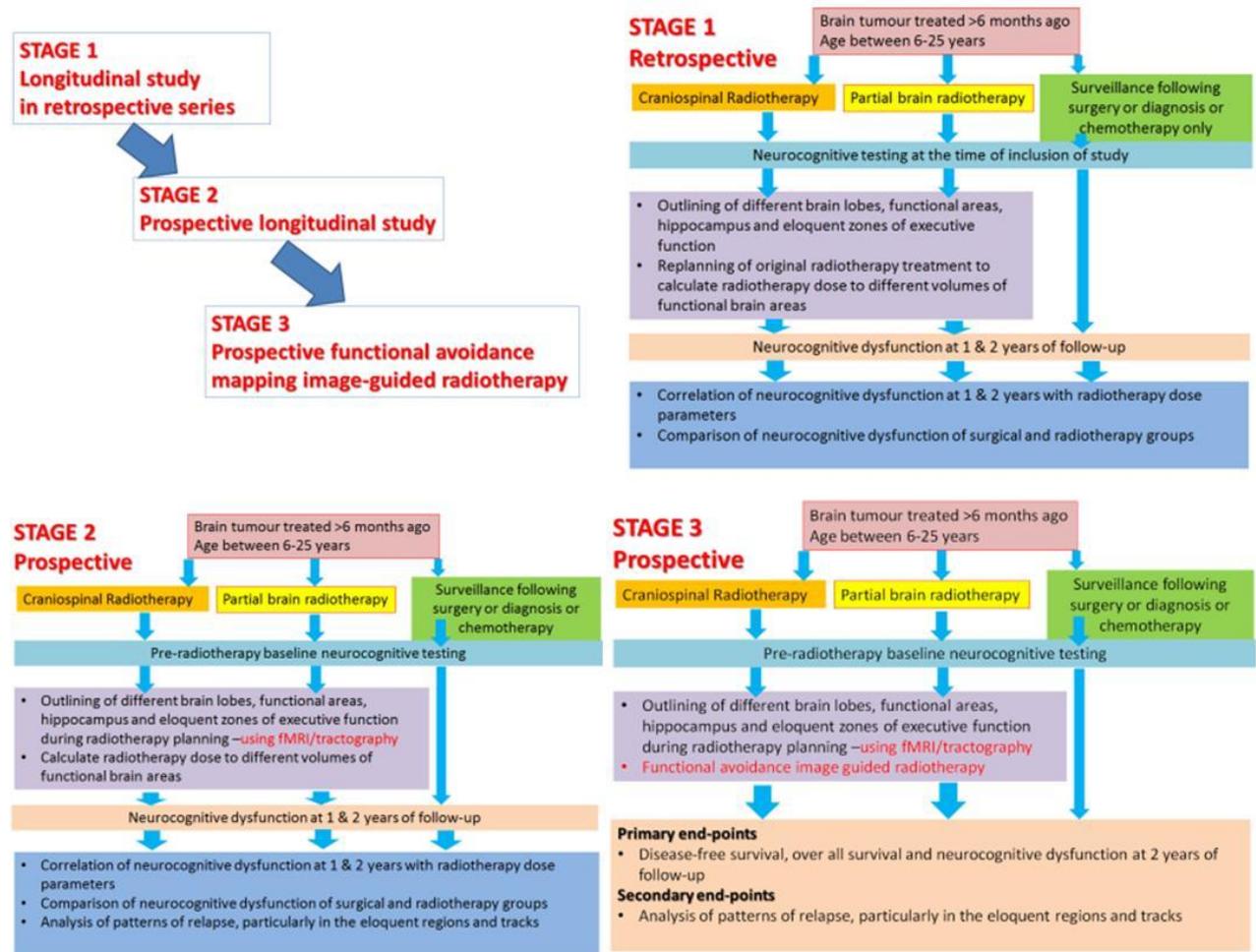


Figure 3 Schematic proposal for a multi-stage approach to develop functional avoiding mapping image-guided radiotherapy for paediatric brain tumour



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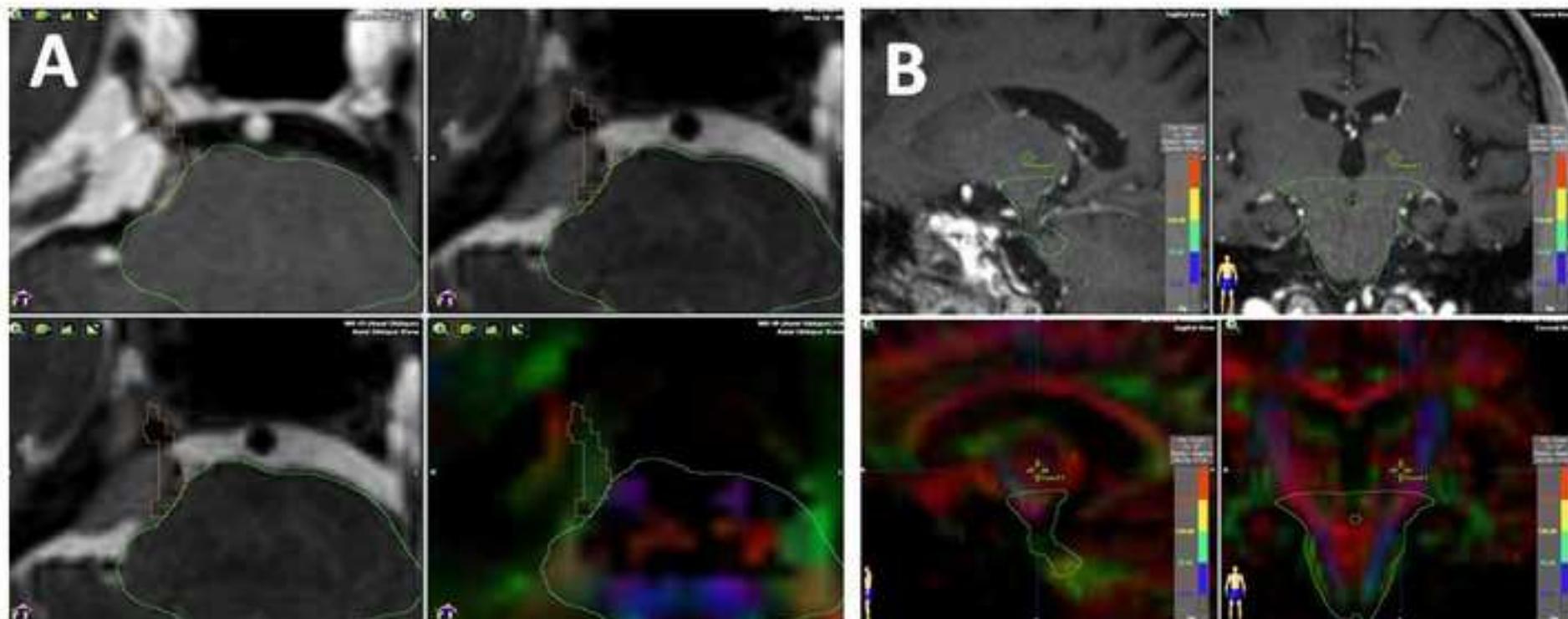
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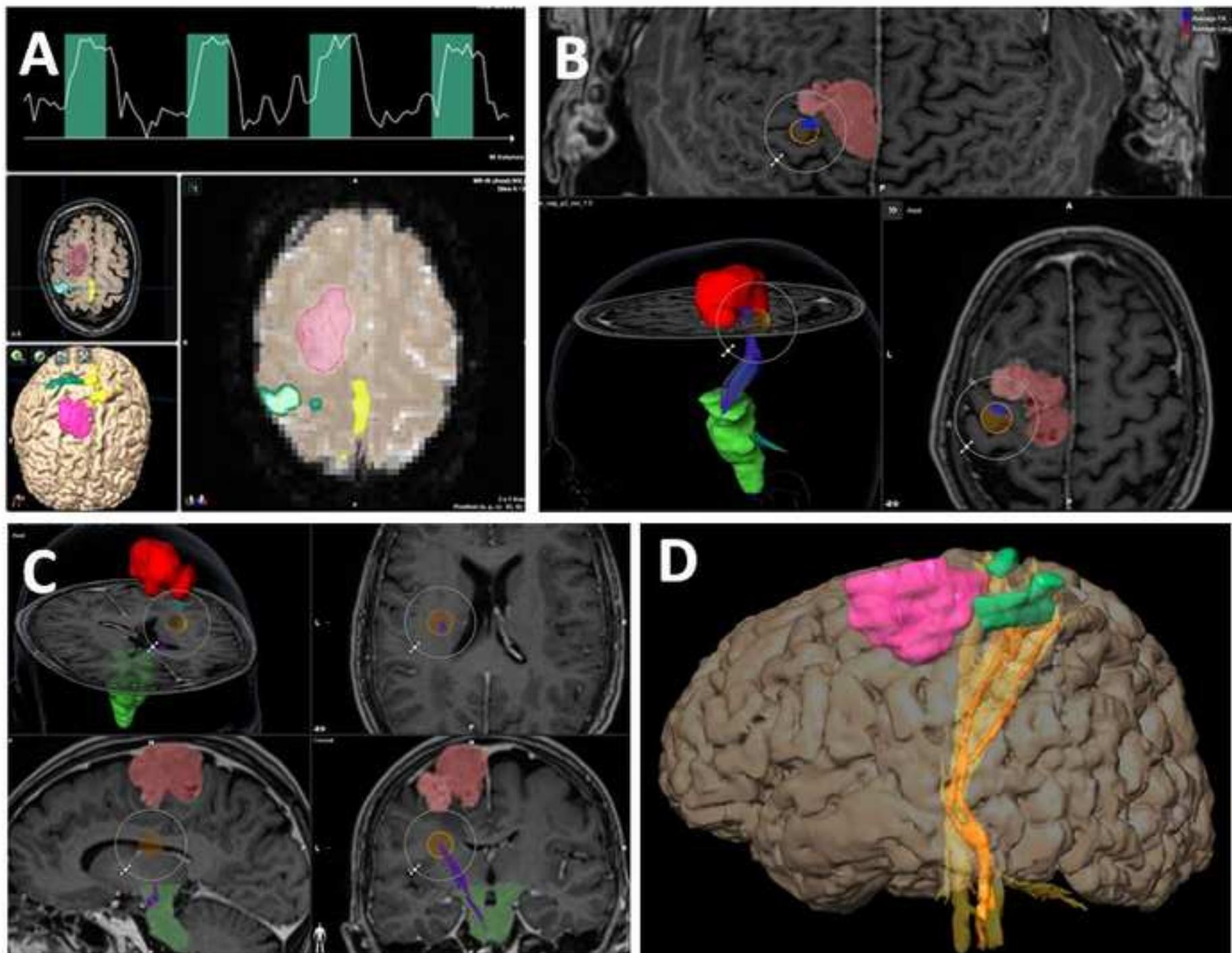
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