PREOPERATIVE AND POSTOPERATIVE DIFFUSION TENSOR IMAGING IN PATIENTS WITH EXTRA-AXIAL LESIONS AT THE FRONTAL OR TEMPORAL REGIONS OF THE BRAIN AND THEIR CORRELATIONS WITH NEUROPSYCHOLOGICAL OUTCOMES

BY

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Dissertation submitted in Partial Fulfillment of the requirement for the Degree of Master of Medicine (Neurosurgery)

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UNIVERSITI SAINS MALAYSIA
2016

THESIS PRODUCED ACCORDING TO NEW USM MANUSCRIPT FORMAT

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Acknowledgements:

- Professor Zamzuri Idris for his constant guidance and mentorship. His priceless advice and encouragement provided the fuel for the inspiration, and motivation for this study.

- Dr Salma @ Win Mar for her assistance in granting access to the radiological facilities used in the study and for her assistance in interpretation of the radiological imaging.

- Puan Wan Azlen Wan Muhamad for her assistance in performing the neuropsychological assessments which were often difficult and time consuming.

- Professor Jafri Malin for has advice and encouragement.

- Cik Amalina who also assisted in the neuropsychological assessments.

- The radiographers in the MRI room, Mr Kew and team who helped facilitate the scans for the patients

- This study was supported by short term grants (ref: 304/PPSP/61312142) from Universiti Sains Malaysia (USM), and approved by Human Research Ethics Committee USM, School of Medical Sciences, Kubang Kerian, Kelantan, Malaysia.

Authors note: This manuscript was prepared for submission to Surgical Neurology International and follows the format for that journal.

Abstract

Background: The underlying changes in the neuronal connectivity adjacent to brain tumours cannot always be depicted by conventional MR imaging. The hypothesis of this study was that preoperative neuropsychological deficits are associated with impairment of diffusivity in association fibre bundles. Hence, we investigated the potential of combined diffusion tensor imaging (DTI) fibre tracking and fractional anisotropy (FA) values of the fibres to determine changes in association fibres and their correlation to neuropsychological scores.

Methods: Our study consisted of eighteen patients with extra-axial brain tumours in areas adjacent to the frontal and temporal lobes. They were assessed pre-and postoperatively with DTI and neuropsychological assessments. MR examinations were performed on a 3T-scanner. FA values were calculated for the uncinate fasciculus, arcuate fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus and corticospinal tracts ipsilateral and contralateral to the tumor. These values were compared with neuropsychological scores for language, memory and attention.

Results: The analysis revealed marked differences in pre- and post-excision of the tumor in both FA values and neuropsychological scores. Quantitative DTI was able to show significant differences in diffusivity of the association fibres before and after the surgery.

Conclusion: The additional use of DTI-fibre integrity and neuropsychological tests may aid in prognostication and decision making prior to surgery.

Keywords: diffusion tensor imaging, brain tumours, neuropsychology, brain mapping, fractional anisotropy.

Abstrak

Perubahan pada sambungan saraf-saraf otak akibat daripada ketumbuhan otak mungkin tidak dapat digambarkan dengan sepenuhnya oleh imej MRI konvensional. Hipotesis kajian ini adalah bahawa masalah neuropsikologi yang dialami pesakit berkaitan dengan ketumbuhan otak sebelum pembedahan ada kaitan dengan kemerosotan dalam difusi pada saraf “association fibres”. Oleh itu, kami berniat untuk mengkaji potensi pengimejan “diffusion tensor imaging” (DTI) dengan nilai “fractional inosotropy” (FA) saraf-saraf “white matter tracts” tersebut dan hubungannya dengan penilaian neuropsikologi. Kami mengkaji lapan belas pesakit yang mempunyai ketumbuhan ”extra-axial” di persekitaran lobar “frontal” dan “temporal”. Mereka dinilai sebelum dan selepas pembedahan dengan DTI and penilaian neuropsikologi. Pemeriksaan MRI dijalankan dengan mesin MRI 3T. Nilai FA dikira untuk “uncinate fasciculus”, ‘superior fronto-occipital fasciculus’, ‘inferior fronto-occipital fasciculus”, dan “corticospinal tract” kedua-dua belah otak. Keputusan ini dibandingkan dengan penilaian neuropsikologi untuk bahasa, pertuturan, ingatan, dan perhation. Analisa yang dilakukan mendapati bahawa terdapat perubahan yang ketara sebelum dan selepas pembedahan pada nilai FA dan juga penilaian neuropsikologi, Penggunaan DTI untuk menilai dan mengkaji saraf-saraf “white matter tracts” ini mungkin dapat membantu dalam ramalan dan perancangan sebelum melakukan pembedahan otak.

Introduction – literature review and rationale for the study

Diffusion tensor imaging (DTI) involves a subset of magnetic resonance imaging that exploits the phenomenon of anisotropy in cellular microstructure to generate quantitative visual depictions of in vivo structure and function of tissue pathways[28]. This method has been widely applied in the study of white matter tracts of the brain with significant insights generated with regard to neural connections and their association with neurological disease, including intracranial tumours[5,15,18]. Diffusion tensor imaging in particular allows a quick, noninvasive, in vivo mapping of white matter tracts and potential patterns of impairment in function and structure. Patterns of impairment of white matter tracts in intracranial tumours have been described such as disruption, inflitration, displacement and widening[24]. Information gained from such tractographic analyses of white matter tracts have been applied clinically to determine maximal safe margins of resection of intracranial tumours with respect to adjacent white matter fibres[33].

The uncinate fasciculus, arcuate fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus are large association white matter tracts involved in language, memory and attention. They connect the prefrontal cortex with the temporal and occipital lobes in the ipsilateral hemispheres and lesions affecting these tracts are may cause a deficit in higher cognitive functions[11,20].

White matter fractional anisotropy (FA) is thought to be related to white matter integrity and decline in FA is often used as an index of decreasing WM health[21]. Mean diffusivity (MD) and fractional anisotropy (FA) are the two most commonly used measures of white matter integrity.

FA refers to the coherence of the orientation of water diffusion, independent of rate. It can calculated as the fraction of total diffusion that can be attributed to anisotropic diffusion, which is derived from the normalized variances of the three eigenvalues[3], with higher values corresponding to a more consistent diffusion orientation. Taken together, a breakdown in white matter integrity would be seen as lower FA[6].

The frontal and temporal lobes have long to be known to play a vital role in speech, memory and attention of normal individuals, more so the dominant hemisphere[8,9,19,29].

Our study is an attempt to quantify the neurologic dysfunction that results from the impairment of major association white matter tracts as defined via diffusion tensor imaging with a standardized neuropsychological assessment, specifically in patients with extra-axial tumours. The utility of neuropsychological assessment in this study lies in the identification of potential deficits that would not be easily acquired via routine bedside neurological examination. Here, we present our results on eighteen patients with intracranial extra-axial tumours located at the frontal or temporal lobes and analyzed their neuropsychological scores for memory, attention and language in relation to their fractional anisotropy values (FA) for uncinate fasciculus (UF), arcuate fasciculus (AF), corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF) and superior fronto-occipital fasciculus (SFOF).

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Bendahari

Tarikh : 25 Julai 2014

Prof. Madya Dr. Zamzuri Idris
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KELANTAN DARUL NAIM

Tuan,

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Sukacita dimaklumkan bahawa Bahagian Penyelidikan & Inovasi, USM telah meluluskan permohonan tuan untuk menjalankan penyelidikan di bawah peruntukan Jangka Pendek seperti berikut:

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Penyelidik Bersama	1. Dr. Win Mar @ Salmah 2. Dr. Ahmad Helmy Abdul Karim 3. Cik Wan Nor Azlen Wan Mohamad	PTJ	1. Pusat Pengajian Sains Perubatan 2. Pusat Pengajian Sains Perubatan 3. HUSM	
Tajuk Projek	Preoperative and Postoperative Diffusion Tensor Imaging in Patients with Intracranial Neoplasms at Frontal or Temporal Regions of the Brain and Their Correlations with Neuropsychological Outcomes for Memory and Attention			
Kluster	Kesihatan & Perubatan	Jumlah Geran		RM37,300.00
No. Akaun	304/PPSP/61312142	Agihan	Tahun 1	RM16,150.00
Tempoh Geran	24 bulan		Tahun 2	RM21,150.00
Tarikh Mula	01 Ogos 2014	Tarikh Tamat	31 Julai 2016	
Senarai peralatan diluluskan	1. Desktop Computer			

2. Kerjasama tuan untuk mengembalikan Borang Perakuan Geran **(Lampiran A)** dalam tempoh **2 minggu** dari tarikh surat ini amatlah dihargai. Bersama-sama ini disertakan juga Garis Panduan Umum Geran Penyelidikan Jangka Pendek **(Lampiran B)** untuk makluman dan tindakan tuan selanjutnya.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"
'Memastikan Kelestarian Hari Esok'

Yang menjalankan tugas,

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Agihan Tahun 1	: RM36,150.00	Tajuk Projek	: *"Preoperative and Postoperative Diffusion Tensor Imaging in Patients with Intracranial Neoplasms at Frontal or Temporal Regions of the Brain and Their Correlations with Neuropsychological Outcomes for Memory and Attention"*
		Kluster	: Kesihatan & Perubatan
		Tempoh	: 2 tahun (01 Ogos 2014 - 31 Julai 2016)
		No. Akaun	: 304/PPSP/61312142

Agihan Projek

Bil	Vot USM	Tahun 1	Tahun 2	Catatan
1.	11000	-	-	
2.	14000	-	-	
3.	21000	-	5,000.00	
4.	22000	-	-	
5.	23000	150.00	150.00	
6.	24000	-	-	
7.	26000	-	-	
8.	27000	-	-	
9.	28000	-	-	
10.	29000	12,000.0	16,000.00	
11.	35000	4,000.00	-	
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Tarikh: 24 JUL 2014

Peralatan yang diluluskan adalah seperti berikut:-

1. Desktop Computer

Preoperative and Postoperative Diffusion Tensor Imaging in Patients with Extra-axial Lesions at the Frontal or Temporal Regions of the Brain and Their Correlations with Neuropsychological Outcomes

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Abstract

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Keywords: diffusion tensor imaging, brain tumours, neuropsychology, brain mapping, fractional anisotropy.

1 Introduction

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2 Materials and Methods

2.1 Subjects

Eighteen patients with extra-axial brain tumours adjacent to the frontal and temporal lobes were assessed pre- and postoperatively with DTI and neuropsychological assessments. The preoperative assessments were done on initial diagnosis prior to starting the patient on steroids. The postoperative assessments were done at 6 weeks after the surgery. The study was approved by the local research and ethics committee (ref: 304/PPSP/61312142) and informed consent was obtained from all subjects.

2.2 DTI study

All MR examinations were performed on a 3T-MRI scanner (Philips Achieva). Mean FA values from three readings were calculated for uncinate fasciculus (UF), arcuate fasciculus (AF), corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF) and superior fronto-occipital fasciculus (SFOF) (Fig. 1) in both cerebral hemispheres. These values were compared with neuropsychological scores for memory, language, and attention.

2.3 Data acquisition

DTI was performed on the whole brain with the following parameters: single shot spin echo planar imaging with TE = 69 ms, TR = 10,190 ms, axial slices, SENSE factor 3.2, number of signals averaged 6, half scan factor 0.712, isotropic 2.2 mm × 2.2 mm × 2.2 mm voxels, b = 0 s/mm^2 plus 15 diffusion-sensitizing gradient directions (b = 800 s/mm^2) and phase encoding in the anterior-posterior direction. Total scan time was 16 min. A T1-weighted scan (3D T1-TFE) was performed as an anatomical reference using identical orientation and slice thickness as the DTI scan. Reconstructed pixel size was 1.9 mm × 1.9 mm for both DTI and T1-weighted images.

2.4 Data processing

DTI data was acquired using the ‘‘FiberTrak’’ package included in the Extended MRI Workspace (EWS) R 2.6.3 (Philips Achieva 3.0T X-series). The DTI data was transferred to a workstation (8GB RAM, 2.33GHz Intel Xeon, Windows 64 bit). This fibre tracking software is based on the ‘‘fibre assignment by continuous tracking’’ (FACT) algorithm. To minimize artifacts caused by movement and eddy currents, coregistration to b = 0 scans was done using the diffusion registration package in the EWS. Fractional anisotropy maps were generated in the EWS. Settings for the tractography were the following: FA > 0.25, maximal angle change 90◦, minimal fibre length 30 mm. Regions of interests (ROIs) were selected to measure the FA values in both hemispheres. The uncinate fasciculus was identified as a white matter tract connecting the medial basal pole of the temporal lobe with the inferolateral part of the basal frontal lobe. The arcuate fasciculus was easily identified at the terminal end of the sylvian fissure deep into the white matter. The corticospinal tract is the fibre tract that runs from the motor cortex (anterior to the central sulcus) down to the posterior limb of the internal capsule. The inferior fronto-occipital fasciculus is the white matter tract that connects the frontal lobe with the occipital lobe and passes through the inner aspect of the insular cortex whilst the superior fronto-oocipital fasciculus was identified as a white matter tract that connects the frontal with the occipital lobe at the medial and superior aspect of the corticospinal tract[17,23,31].

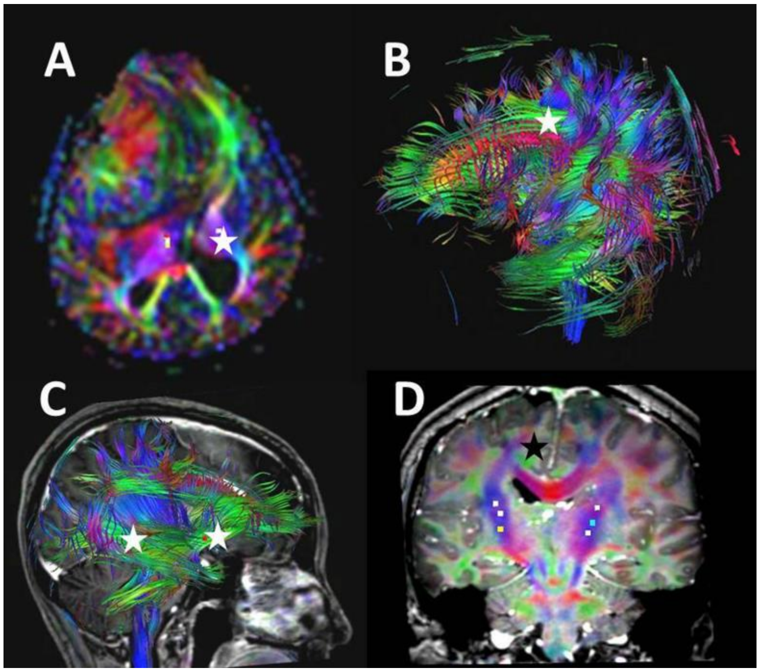

Figure 1: The studied white matter tracts are identified using FA map and DTI fibre-tracking. A: the white star indicates the corticospinal tract; B: the white star indicates the arcuate fasciculus; C: the white star anteriorly located signifies the uncinate fasciculus whilst the posterior one indicates the inferior fronto-occipital fasciculus and D: the black star indicates the superior fronto-occipital fasciculus.

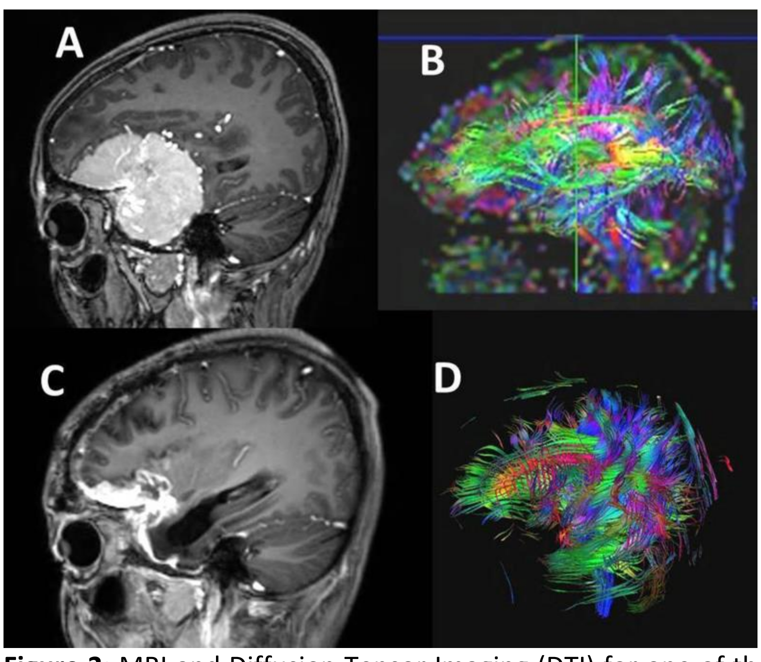

Figure 2: MRI and Diffusion Tensor Imaging (DTI) for one of the studied patients. A and B: MRI and DTI prior to surgery and C and D, the MRI and DTI after the surgery. Marked improvements are noted in anatomical as well as in tensor strength.

2.5 Neuropsychological tests

The neuropsychological tests applied for this study are divided into 3 main components: memory, attention and language assessments. The memory tests were for the immediate, delayed, auditory and total memory. The attention test used was Comprehensive Trail Making Test (CTMT) and for the language assessments, the batteries of tests were for visual naming, sentence repetition, controlled oral word association, oral spelling, written spelling, block spelling, token test, aural and reading comprehension[14,25]. The actual tests carried out were Wechsler Abbreviated Scale of Intelligence, Wechsler Memory Scale (abbreviated), Rey Auditory Verbal Learning Test, Benton Visual Retention Test, Comprehensive Trail Making Test and Multilingual Aphasia Examination.

2.6 Surgery

All the patients included in this study were operated on in Hospital Universiti Sains Malaysia. The operating surgeon in all cases was Professor Dr Zamzuri Idris, and assisted by various registrars from the department of Neurosurgery.

2.7 Statistical method

Inferential Statistical analysis was performed with the use of commercially available software SPSS Inc. Version 20. Probability values < 0.05 were considered significant. Analysis based on Wilcoxon-signed rank test (non-parametric test) for the significant difference between pre and post results (p-value $< .05$).

3 *Results*

3.1 Demographic data of the study

Eighteen patient's data were analyzed for demography, clinical condition, neuropsychological impairments, and the FA values of the white matter tracts. There were 11 female and seven male patients with age ranging from 22 to 64 years of age (mean age of 47.22 years) of which only one was left handed. Sixteen of these patients had a tumour compressing on the left side of the brain, and the remaining 2 patients had a tumour on the right. All tumours were successfully removed with Simpson's grading of 1 or 2 with resolution of symptoms in all patients after the surgery (Simpson Grading for meningiomas surgery: Grade I - complete removal including resection of underlying bone and associated dura; Grade II - complete removal and coagulation of dural attachment; Grade III - complete removal without resection of dura or coagulation; Grade IV - subtotal resection)[2]. Further analysis was made for neuropsychological scores together with fractional anisotropy values for all studied-white matter tracts in these eighteen patients and is depicted below in table 1.

Table 1: Summary of the patients' demographic data detailing the age, sex, tumour side, handedness, Simpson grading, and clinical outcome of the patients

Case	Age	Sex	Tumor Side	Handedness	Simpson Grading	Neuropsychological Outcomes
1	48	F	L	R	I	Y
2	56	F	L	R	I I	Y
3	32	M	R	R	I I	Y
4	46	M	L	R	I	Y
5	53	M	L	R	I I	Y
6	26	F	L	R	I I	Y
7	22	F	L	R	I	Y

8	32	M	R	R	I	Y
9	57	M	L	R	I I	Y
10	55	M	L	R	I	Y
11	63	M	L	R	I I	Y
12	51	F	L	L	I I	Y
13	24	F	L	R	I	Y
14	57	F	L	R	I I	Y
15	49	F	L	R	I	Y
16	53	F	L	R	I I	Y
17	62	F	L	R	I I	Y
18	64	F	L	R	I I	Y
Age in years; F - Female; M - Male; L - Left; R – Right; Y- Improvement in Neuropsychology scores; N- No improvement in Neuropsychology scores						

3.2 Component of neuropsychological outcomes and FA values

Table 2 below shows the results in all the 18 parameters measured during neuropsychological assessment before and after surgery for 18 parameters tested, with p-value < 0.05 statistically significant. The patients show a statistically significant improvement in all the parameters tested following surgery.

Table 2: Pre and post-operative neuropsychological assessments analysis

Measures	Pre		Post		^p-value
	Mean	SD	Mean	SD	
Full-2 IQ	75.56	17.212	86.11	18.026	.002*
Immediate Memory	70.44	17.002	82.56	19.954	.001*
Delayed Memory	72.00	17.974	84.67	20.243	.000*
Total Memory	70.28	16.552	84.39	18.092	.000*
Visual Memory Correct Score	4.17	2.956	6.83	2.662	.001*
Visual Memory Error Score	8.94	6.197	4.94	4.659	.000*
CTMT Executive Function	21.13	6.109	24.13	4.031	.022*
Auditory Immediate Recall	30.33	16.866	41.56	17.113	.000*

Auditory Delayed Recall	10.11	9.952	17.17	8.291	.001*
Visual Naming	34.76	12.357	46.39	7.237	.000*
Sentence Repetition	7.00	3.354	9.00	3.010	.032*
Controlled Oral Word Association	26.53	15.855	31.56	10.929	.046*
Oral Spelling	8.35	3.499	10.00	3.029	.004*
Written Spelling	8.53	3.573	10.00	2.870	.012*
Block Spelling	7.76	3.784	9.33	3.464	.010*
Token Test	32.88	12.232	38.50	8.403	.001*
Aural Comprehension	13.47	4.989	16.22	1.957	.005*
Reading Comprehension	14.41	5.767	17.17	2.684	.002*

^Analysis based on Wilcoxon-signed rank test (non-parametric test)
*Significant difference between pre and post results (p-value < .05)

3.3 FA values for the pre and postoperative white matter tracts

As shown in Table 3 all measurements for the tracts in the left hemisphere demonstrated improvement and statistically significant results with p-value < 0.05, however only one out of the five tracts in the right cerebral hemisphere demonstrated significant difference shown on the inferior occipto-temporal (right) with p-value = 0.016, and the remaining parameters such as uncinate tract (right), arcuate fasciculus (right), corticospinal tract (right) and superior fronto-occipital (right) with p-value > 0.05. This could be due to a majority of the tumours presenting on the left, and thus causing the tracts in the left hemisphere to be more significantly affected while having minimal effects on the tracts in the right hemisphere. From the analysis we can surmise that there were statistically significant improvements in FA values of the white matter tracts which represent the integrity of the white matter fibres following removal of the tumour. There was also a statistically significant improvement in the neuropsychological scores for these patients. These changes seemed to contribute towards clinical as well as neuropsychological improvements in memory, attention and language. This may indirectly suggest that the brain networks for the whole brain are returning to a healthy state.

Table 3: Pre- and post operative White Matter Tract results, FA values of 5 tracts from both cerebral hemispheres have been measured.

Measures	**Pre**		**Post**		**^p-value**
	Mean	**SD**	**Mean**	**SD**	
Uncinate tract (right)	0.519	0.112	0.536	0.115	.053
Uncinate tract (left)	0.416	0.072	0.443	0.069	.003*
Arcuate fasciculus (right)	0.627	0.048	0.641	0.035	.102
Arcuate fasciculus (left)	0.484	0.164	0.524	0.164	.003*
Corticospinal tract (right)	0.698	0.131	0.696	0.106	.332
Corticospinal tract (left)	0.603	0.142	0.627	0.136	.017*
inferior fronto-occipital (right)	0.722	0.132	0.745	0.147	.016*
inferior fronto-occipital (left)	0.605	0.110	0.690	0.104	.005*
Superior fronto-occipital (right)	0.616	0.068	0.625	0.106	.072
Superior fronto-occipital (left)	0.452	0.205	0.513	0.142	.007*

^Analysis based on Wilcoxon-signed rank test (non-parametric test)
*Significant difference between pre and post results (p-value < .05)

3.4 FA lobes and outcomes

FA values of the lobes of the brain were also measured as shown in Table 4. The FA values of the right and left frontal, parietal, temporal (medial and lateral) and occipital lobes were derived, where the results show statistically significant improvement for both right and left lobes with p-value < 0.05 for all 18 subjects. Frontal, parietal, temporal, and occipital lobe regions were defined so as to be consistent with the automated anatomic labeling (AAL) structures defined by Tzourio-Mozoyer et al (2001) and further defined by Grieve et al (2007)[12,30].

Table 4: Pre and post-operative FA values as defined by the different lobes

Measures	Pre		Post		^p-value
	Mean	SD	Mean	SD	
Right frontal	0.335	0.094	0.347	0.094	.000*
Right parietal	0.313	0.065	0.330	0.070	.006*
Right temporal (medial)	0.286	0.102	0.316	0.111	.010*
Right temporal (lateral)	0.302	0.086	0.334	0.084	.000*
Right occipital	0.287	0.045	0.303	0.049	.029*
Left frontal	0.340	0.084	0.361	0.085	.003*
Left parietal	0.346	0.095	0.375	0.103	.012*
Left temporal (medial)	0.344	0.056	0.366	0.095	.004*
Left temporal (lateral)	0.334	0.072	0.357	0.087	.006*
Left occipital	0.326	0.065	0.350	0.083	.023*

^Analysis based on Wilcoxon-signed rank test (non-parametric test)
*Significant difference between pre and post results (p-value < .05)

4 Discussion

4.1 Clinical outcomes and white matter tracts

For our study we explored the effect of main association white matter tracts and cognitive performance in patients with tumours compressing on the frontal or temporal lobes of the brain. We chose ROI-based analyses because of its superior validity compared to voxel-based or deformation based approaches at present. We focused on the long association fibre tracts because they represent important connections of the cortico-cortical and limbic-association cortical networks which are known to play a major role in cognitive functioning and language[10]. The fibre tracts integrity was quantified by anisotropy measurements within the arcuate fasciculus, uncinate fasciculus, superior fronto-occipital fasciculus and inferior fronto-occipital fasciculus. Muller et al previously demonstrated a normal distribution as well as a fairly good reliability and precision of ROI-based DTI measurements using FA values[26].

We assessed eighteen patients in this study, and as shown in Table 1 there was a fairly wide age distribution among the patients (22-64 years), while there was slight female preponderance (11 female vs 7 male). The majority of the patients were right handed (17 vs 1) while most of the tumours were left sided (16 vs 2). They all underwent a craniotomy and we managed to achieve tumour excision Simpson grade I and II in all of our patients studied, and for the duration of the study none of them required a second surgery. All of the patients had shown improvement after the surgery as evidenced by the improvement in neuropsychological scoring assessments.