Neurobehavioural changes in patients following brain tumour: patients and relatives Perspective

N Gregg[1], A Arber[2], K Ashkan[3], L Brazil[4], R Bhangoo[3], R Beaney[4], R Gullan[3], V Hurwitz[3], A Costello[5*#], L Yágüez[1,5,#]

[1] King's College London, Department of Psychology, Institute of Psychiatry, UK

[2] School of Health and Social Care, University of Surrey, Guildford, UK

[3]Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London, UK

[4]Department of Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK

[5] Neuropsychology Department, King's College Hospital NHS Foundation Trust, London, UK

[#]joint senior authors

*corresponding author: Dr Angela Costello, Neuropsychology Department, 9th Floor Ruskin Wing, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK. Tel: +44 0203 299 8330; fax: +44 0203 299 8351

ABSTRACT

Purpose: Patients and relatives experiences of behavioural and personality changes following brain tumour were assessed to determine whether these changes are more prominent in the experience of patients with frontal tumours and their relatives as a first step to evaluate the need to develop appropriate support and management of such changes, which have a substantial impact on social functioning, and ultimately to improve quality of life.

Methods: Patients and relatives rated the patients' current levels of apathy, disinhibition and executive dysfunction on the Frontal Systems Behaviour Scale. Patients also completed the Hospital Anxiety and Depression Scale. The data from 28 patients with frontal tumours and 24 of their relatives, and 27 patients with non-frontal tumours and 25 of their relatives, were analysed.

Results: Patients with frontal tumours rated themselves significantly higher than patients with non-frontal tumours on all frontal systems-related behaviours. The number of patients reporting *clinical* levels of difficulty was significantly greater in patients with frontal tumours for disinhibition. The ratings of relatives of patients with frontal tumours were significantly higher than those of relatives of patients with non-frontal tumours for apathy. *Clinically* significant levels of apathy and executive dysfunction were however reported by at least 40% of patients and relatives regardless of tumour location. *Clinical* levels of anxiety were reported by significantly more patients with frontal tumours than those with non-frontal tumours.

Conclusion: Support and management of behavioural and personality change for patients with brain tumours and their relatives, regardless of tumour location, would be most appropriate.

INTRODUCTION

Brain tumours not only give rise to a range of neurological and physical deficits but also may result in personality and behavioural changes. Thus the social impact of brain tumour has particular significance. Difficulties with personality and social behaviour have been consistently reported following damage to the frontal lobes [1-4] including lack of insight into these personality changes. Relatives of patients with brain tumours report personality change to be one of the factors associated with poor quality of life[5,6]. Although personality change is a well-recognized symptom of brain tumour, there are very few studies specifically concerned with the impact of a brain tumour on personality and social dysfunction in daily life and within the family.

Increasingly evidence suggests that different anatomical regions of the frontal lobes mediate different aspects of social behaviour [7]. Lesions in the orbitofrontal cortex are associated with emotional lability and mood disturbances [8,9]. Social awareness can also be significantly affected, with patients showing reduced concern about or insight into the consequences of their behaviour and/or reduced empathy for the impact of their behaviour on others[10]. The orbitofrontal cortex also appears important in adhering to social rules and conventions; lesions in this area have been associated with disinhibited and socially inappropriate behaviour[11]. The dorsolateral cortex plays an important role in mediating executive cognitive functions, such as working memory, inhibition, flexibility, problem-solving, planning, goal-setting, initiation and strategy generation [12,13]. The medial prefrontal cortex is associated with motivational aspects of behaviour; lesions here can result in apathy[14].

Personality and behavioural change can have devastating functional consequences resulting in reduced personal autonomy, unemployment and/or divorce. Executive difficulties with organising, initiating, directing, monitoring and controlling interpersonal behaviour can make it difficult to function personally and professionally[15,16]. Despite what can be drastic

personality changes, patients with frontal tumours may be unaware that their behaviour has changed or is socially inappropriate [17,10].

Aims

The primary aim of this study was to measure patients and relatives assessment of behavioural and personality changes following diagnosis of the brain tumour and whether these changes are more prominent in the experience of patients with brain tumours involving the frontal cortex and their relatives. Identifying which groups of patients and/or relatives are more likely to report significant changes in personality and behaviour can enable targeted provision of appropriate support.

As the frontal lobes play an important role in self-awareness and self-monitoring, it was also expected that patients with frontal tumours would show reduced insight into their levels of social cognitive functioning compared to their relatives.

METHODS

Sixty-six adult patients with focal frontal brain tumours and their relatives and 60 adult patients with focal tumours not involving the frontal cortex and their relatives were asked to participate. All participants were recruited from the Joint Multi-Disciplinary Neuro-Oncology Clinic. The inclusion criteria were: i) aged 18 years or above, ii) able to give consent, iii) having undergone surgery to confirm diagnosis.

There were no exclusion criteria for relatives, the majority (73.4%) of whom were the spouse/partner of the patient; 14.3% were the mother/father; 4.1% sister of the patient; 4.1% the son and 4.1% the non-relative carer. Demographic and clinical background information was obtained for patients from their medical records (see table 1). The majority of patients in both the frontal and nonfrontal tumour groups had low-grade tumours (75 and 81% respectively). Lesion localisation was determined on the basis of MRI scan and report from the senior neuroradiologist. The temporal and parietal lobes were the most common locations for non-frontal tumours, each diagnosed in 33.3% of patients, and 11.1% had temporal-parietal tumours. All except two of the nonfrontal brain tumour patients had undergone

surgery. Thirteen frontal tumour patients had radiotherapy, 7 of these patients also received chemotherapy. Of the 13 nonfrontal patients that had radiotherapy, one also underwent chemotherapy. All participants gave written informed consent prior to participating in the study.

Table 1: Demographic and clinical features of patients

	Frontal Patients (N=28)	Non-Frontal Patients (N=27)
Age years (mean, SD, Range)	50.3 (13.09) 34-75	48.33 (15.10) 21-73
Male/Female	11/17	11/16
Time since surgery years (mean, SD, Range)	4.82 (3.04) 2-17	4.50 (2.98) 1-14
Tumour location		
➢ Left	14	12
➢ Right	13	14
➢ Bifrontal	1	-
➢ Subcortical	-	1
Tumour Grade		
➢ 1	5	5
➢ 2	16	17
➢ 3	4	3
➢ 4	3	2

Patients were asked to complete the Frontal Systems Behaviour Scale (FrSBe) and the Hospital Anxiety and Depression Scale (HADS). Relatives were asked to complete only the FrSBe. Questionnaires were posted to patients and relatives in separate envelopes along with stamped addressed envelopes for the return of completed questionnaires.

The Frontal Systems Behaviour Scale [18] is a 46-item behaviour rating scale designed to identify and quantify behaviours frequently reported following damage to the frontal systems of the brain. It consists of a Self-Rating Form for completion by the patient, and a Family

Rating Form completed by a relative who knows the patient well. Respondents are asked to rate the current frequency of behaviours (e.g. (Apathy):'Speaks only when spoken to'; (Disinhibition) 'Talks out of turn, interrupts others in conversations'; (Executive Dysfunction) 'Cannot do two things at once') according to a 5-point Likert-type scale, where 1 = almost never, 2 = seldom, 3 = sometimes, 4 = frequently and 5 = almost always. Each rating form generates a total score derived from three subscales measuring apathy, disinhibition and executive dysfunction. The FrSBe provides a measure of behaviour both before (i.e. premorbid) and after brain damage.

The FrSBe provides normative data for age, gender and education level for individual subscale scores and for the Total Score. Raw scores were converted to T Scores (linear transformations of the scores obtained in the normative sample, such that the distribution of FrSBe scores has a mean of 50 and Standard Deviation of 10). T scores at or above 65 represent *clinically* significant levels of symptomatology and T scores of 64 or less indicate non-clinical levels. T scores of between 60 and 64 may be interpreted as an indication of borderline levels of impairment. For the purpose of the current study, borderline scores were classified as '*clinical*' as having more than 2 levels of classification would result in insufficient power for the statistical analyses.

The Hospital Anxiety and Depression Scale (HADS)[19]), was given to measure depressed mood, as this has been found to be common in patients with brain tumours and because of the behavioural similarities between the syndromes of apathy and depression[20,21]. Although less studied in cancer populations, anxiety has also been shown to be prevalent among oncology patients [22]. The HADS is a 14-item self-report questionnaire and consists of an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), each containing 7 intermingled items. Cut-off scores are provided, enabling levels of anxiety and depression to be classified as normal, mild, moderate or severe. Scores of <8 classified as 'normal', scores 8-10 as 'mild', scores of 11-15 as 'moderate' and scores of 15-21 as 'severe'. For the purpose of the current study, normal scores were classified as 'non-clinical' and mild, moderate and

severe scores as '*clinical*', as having more than two levels of classification would result in insufficient power for the statistical analyses.

Response rates for patients with frontal tumours and their relatives were 42 and 36%, respectively, and for patients with nonfrontal tumours and their relatives' response rates were 45 and 42% respectively. Thus, a total of 28 patients with frontal tumours and 24 of their relatives completed the questionnaires, of which there were 23 complete patient-relative pairs. A total of 27 patients with tumours not involving the frontal cortex and 25 of their relatives completed the questionnaires, of which there were 22 patient-relative pairs.

Statistical analysis

Paired *t* tests were conducted to compare premorbid with post-illness overall ratings on the FrSBe for the frontal and non-frontal patient groups and the respective relatives groups (see table 2). Hochberg [23] corrections were applied to control for type I errors in multiple comparisons.

Table 2: FrSBe Total mean rating scores (SD) premorbid and post-illness

Group	N	Premorbid	Post-illness	P value* (1-tailed)
Frontal	28	92.89 (26.11)	107.14 (29.43)	0.026
Non-frontal	27	79.25 (18.31)	89.59 (26.12)	0.001
Frontal Relatives	24	83.83 (22.11)	100.41 (31.25)	0.024
Non-frontal Relatives	25	79.84 (21.49)	89.28 (23.54)	0.000

*Hochberg adjusted p values

Post-illness One-way, independent groups, analyses of variance (ANOVA) were conducted to compare levels of apathy, disinhibition, executive function and overall frontal systems-related

behaviour reported by patients and their relatives (see Table 3). To examine whether frontal patients showed reduced insight, one-way independent groups (relatives of patients with frontal tumours vs. patients with frontal tumours and relatives of patients with nonfrontal tumours vs. patients with nonfrontal tumours) ANOVAs were conducted to compare FrSBe ratings by patients and by their relatives for each frontal systems-related behaviour. Only data obtained from complete 'patient-relative pairs' were included in these analyses. Clinical vs. nonclinical levels on all the measures of the FrSBe for the patients and relatives groups were assessed by 2x2 chi-square tests. One-way, independent groups, ANOVAs were performed to compare levels of depression and anxiety reported by patients with frontal tumours and those with nonfrontal tumours. In addition, normative test data comparisons were used to classify patients' HADS scores as 'clinical' or 'nonclinical', and 2x2 chi-square tests were performed to compare the number of patients with frontal tumours with the number of patients with nonfrontal tumours reporting clinical levels of anxiety and depression.

Apart from the paired t tests 9where post-illness overall FrSBe score was predicted to be higher than premorbid score for all groups), all statistical tests were two-sided with statistical significance set at the 0.05 level.

Results

Premorbid vs. post-illness FrSBe rating scores

As expected, the total FrSBe scores for the frontal and nonfrontal patient groups and both relatives groups were significantly higher post-illness (See Table 2).

Post-illness FrSBe rating scores

Patients with frontal tumours reported significantly higher levels than patients with non-frontal tumours on all measures; apathy, $F(1, 53) = 4.44$, $p = 0.04$; disinhibition, $F(1, 53) = 4.90$, $p = 0.031$; executive dysfunction, $F(1, 53) = 4.10$, $p = 0.048$; and total score (overall frontal systems-related behaviour), $F(1, 53) = 5.46$, $p = 0.023$ (see Table 3).

The comparisons of 'patient-relative pairs' showed no significant difference on any measure between the frontal patients group and their relatives or between nonfrontal patients group and their relatives.

Table 3: FrSBe mean rating scores (standard deviations)

	Frontal Tumours		Non-Frontal Tumours	
FrSBe Score	Patients	Relatives	Patients	Relatives
Apathy	33.89 (10.78)	32.04 (12.64)	28.0 (9.92)	25.80 (7.58)
Disinhibition	31.54 (8.36)	28.17 (6.84)	26.74 (7.68)	25.68 (7.69)
Executive Dysfunction	41.71(12.97)	40.20 (14.54)	34.85 (12.14)	37.80 (10.99)
Total Score	107.14(29.43)	100.42(31.26)	89.59 (26.13)	89.28 (23.55)

Clinical levels of frontal systems related behaviour

The number and percentage of patients and relatives in each group reporting clinical or nonclinical levels of frontal systems-related behaviours according to their FrSBe rating are presented in Table 4.

There was a trend for more patients with frontal tumours than patients with nonfrontal tumours to report clinical levels of al behaviours measured and this reached statistical significance for disinhibition: $X^2 = 5.973$, df = 1, and p = 0.015 (see figure 1).

Although there was a trend for more relatives of patients with frontal tumours than relatives of patients with non-frontal tumours reporting *clinical* levels of apathy and disinhibition this did not reach statistical significance (see figure 1).

Although there was a trend for more relatives of patients with nonfrontal tumours than their relatives to report clinical levels of disinhibition, this did not reach statistical significance, and there were no significant differences between these patients and their relatives on the other measures.

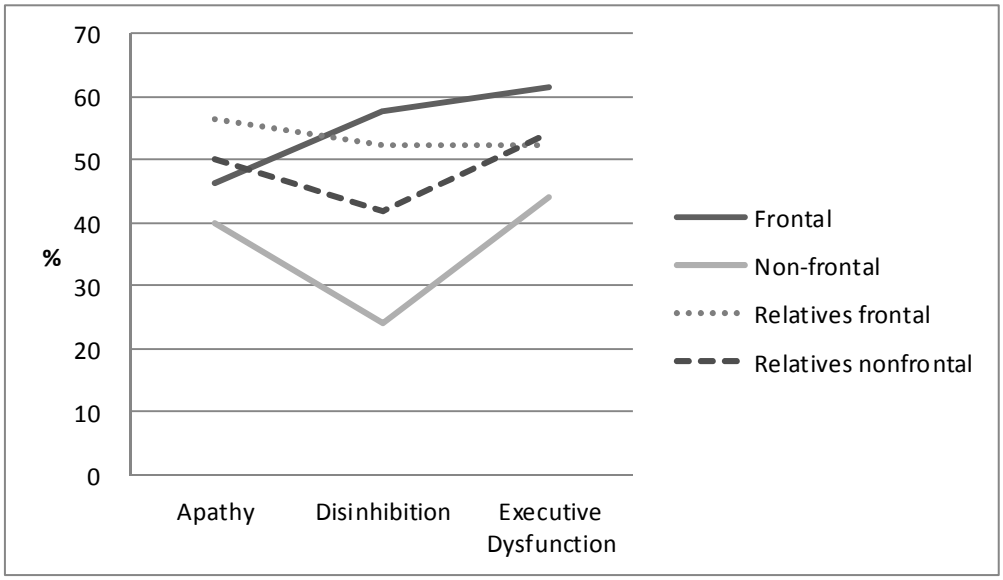

Fig.1 Percentage of patients with *clinical* levels of Apathy, Disinhibition and Executive Dysfunction as rated by patients and relatives

Depression and Anxiety Scores

Patients with frontal tumours scored significantly higher for depression than patients with nonfrontal tumours F (1, 52) = 6.35, $p = 0.015$. There were no significant difference in anxiety scores (see Table 5).

There was no significant difference in the number of patients with frontal tumours and patients with non-frontal tumours reporting *clinical* levels of depression, but significantly more patients with frontal tumours than patients with non-frontal tumours reported *clinical* levels of anxiety ($X^2 = 8.927$, df = 1, p = 0.003).

Table 4 Number and % of frontal and non-frontal tumour patients and their respective relatives reporting *clinical* or non-clinical levels of frontal systems-related behaviours on the FrSBe.

	Apathy		Disinhibition		Executive Dysfunction		Total	
	Clinical	Non-Clinical	Clinical	Non-Clinical	Clinical	Non-Clinical	Clinical	Non-Clinical
Frontal Patients (n=26)								
N	12	14	15	11	16	10	15	11
%	46.2	53.8	57.7	42.3	61.5	38.5	57.7	42.3
Non-Frontal Patients (n= 25)								
N	10	15	6	19	11	14	11	14
%	40	60	24	76	44	56	44	56
Relatives of Frontal Patients (n=23)								
N	13	10	12	11	12	11	15	8
%	56.5	43.5	52.5	47.8	52.2	47.8	65.2	34.8
Relatives of Non-Frontal Patients (n=24)								
N	12	12	10	14	13	11	11	13
%	50	50	41.7	58.3	54.2	45.8	45.8	54.2

Two frontal tumour patients; 2 non-frontal patients; 1 relative of frontal tumour patient and 1 relative of non-frontal tumour patient were not included in the above analyses due to missing education data.

DISCUSSION

Pre and post-illness changes in frontal systems-related behaviour were analysed. As expected, patients with frontal tumours and patients with non-frontal tumours and their respective relatives report significantly higher levels of overall frontal-system related behaviour post-illness.

Post-illness, patients with frontal lobe tumours reported significantly higher levels of apathy, disinhibition and executive dysfunction than patients with non-frontal brain tumours. Normative comparisons revealed an overall trend for a greater percentage of frontal than non-frontal patients to report *clinical* levels of apathy, disinhibition and executive dysfunction, which reached statistical significance for disinhibition. These findings indicate that the subjective experience of difficulties with personality and behavioural change is greater for patients with frontal tumours than patients with non-frontal tumours and support the evidence that the frontal lobes play a key role in mediating various aspects of social functioning [4,11]. Furthermore, patients with frontal brain tumours had significantly higher *clinical* levels of disinhibition suggesting that these patients had more problems with inhibitory control.

Importantly, while patients with frontal tumours reported significantly higher levels of all behaviours, and a trend was observed for more *clinical* levels of all frontal-systems-related behaviours in patients with frontal tumours than patients with non-frontal tumours, *clinical* levels of apathy and executive dysfunction were also reported in at least 40% of patients with non-frontal tumours. Thus, for a substantial proportion of patients with brain tumours there are changes in personality and behaviour, regardless of tumour location. This supports the view that although the prefrontal cortex has a critical role in social functioning, the integrity of other regions of the brain is necessary for optimal functioning [24]. However, as disinhibition was reported in a relatively small proportion (24%) of patients with non-frontal tumours, this suggests that disinhibition is more specifically associated with damage to frontal areas of the brain. This lends support to a recent study examining the neural correlates of socioemotional disinhibition and executive function in older patients with neurodegenerative disease which reported a specific association between orbitofrontal areas and disinhibition [25].

Regarding relatives' subjective experience of personality and behavioural change following brain tumour there was a trend for the relatives of patients with frontal tumours to report higher levels of all frontal-systems related behaviour than relatives of those with non-frontal tumours. Interestingly, while this trend was significant for all behavioural measures for the

frontal patient group, for the relatives of frontal patients this was only significant for apathy. Although the behavioural symptoms of apathy and depression can be similar, apathy is best characterised as a disorder of motivation rather than mood state per se. Thus, the disturbance of mood (e.g. sadness) which is a predominant feature of depression is either absent or only a minor feature in frontal systems related apathy[18]. While the frontal brain tumour patients had a higher overall score on the depression subscale of the HADS there was no significant difference in the number of patients reporting *clinical* levels of depression between the two patient groups. Therefore, the higher levels of apathy reported by the relatives of the frontal brain tumour patients is less likley to merely reflect higher levels of depression in these patients.

Although there was an overall trend for more relatives of patients with frontal tumours than relatives of patients with non-frontal tumours to report *clinical* levels of apathy and disinhibition, these differences did not reach statistical significance. However, *clinical* levels of frontal systems-related behaviours were reported by at least 40% of all relatives, suggesting that the subjective experience of brain tumour for a substantial proportion of relatives involves *clinically* significant difficulties with personality and behavioural changes, regardless of whether tumour location was frontal or non-frontal.

It was expected that patients with frontal tumours would show reduced insight into their levels of personality and behavioural changes compared to their relatives. However, no significant difference was found on any behavioural measure between ratings by patients with frontal tumours and by their relatives or between patients with non-frontal tumours and their relatives. One explanation could be that as reduced insight into one's behaviour is considered to be particularly associated with the orbitofrontal cortex [26], this would support the contention of precise and dissociable networks between distinct regions and specific distant brain regions [27]. In other words different parts of the orbitofrontal cortex are differentially involved in insight and disinhibition.

Table 5 HADS anxiety and depression scores (means and standard deviations) and number and percentage of patients classified as having *clinical* and non-clinical levels of depression and anxiety

HADS Score	Frontal Patients (n=28)	Non-Frontal (n=26)	Total Patients (n=54)
Depression	6.07 (4.38)	3.42 (3.20)	
➢ *Clinical*	8(28.5%)	4(15.3%)	12 (22.2%)
➢ Non-clinical	20 (71.4%)	22 (84.6%)	42 (77.7%)
Anxiety	9.11 (4.52)	6.88 (3.94)	
➢ *Clinical*	20 (71.4%)	8(30.7%)	28 (51.9%)
➢ Non-clinical	8(28.5%)	18 (69.2%)	26 (48.1%)

One non-frontal patient did not complete the HADS

Patients with frontal tumours reported significantly higher levels of depression, although the rate of *clinical* levels of depression was not significantly greater than for patients with non-frontal tumours. This however may reflect the relatively small number of patients with *clinical* levels of depression in both groups (frontal patients n =8; non-frontal patients n=4). Depression is an important complication of primary cerebral glioma and is associated with reduced quality of life.[20] Our rate of depression in patients with frontal tumours was similar to the overall patient-rated measures reported in the review by Rooney *et al* [20](i.e. 28.5% vs 27% respectively). Of the 10 studies that used the HADS depression subscale, the mean scores in these studies ranged from 3.15 to 6.2. The mean score for patients with frontal tumours in our study was 6.1 which is higher than all but one of the studies reported by Rooney *et al*.[20]. For our non-frontal patients the mean score on the HADS depression subscale was lower than all but one of the studies reported by Rooney *et al*. [20]. Although there is currently no consistent evidence that tumour location and depression are associated, the study by Wellisch *et al* [28] reported that frontal lobe tumour location was independently associated with major depressive disorder using DSM-IV criteria. Our findings lend support to a possible relationship between tumour location and depression. However, larger studies

investigating the frequency of depression in patients with primary brain tumours are required to elucidate the potential association of tumour location in the aetiology of brain-tumour associated depression.

Although we found no significant difference in the overall scores on the HADS anxiety subscale between the frontal and non-frontal patient groups when the scores were classified as *clinical* and non-clinical, significantly more frontal tumour patients than non-frontal tumour patients had *clinical* levels of anxiety. Indeed over 71% of the frontal tumour patients reported *clinical* levels of anxiety compared with 30.7% of the non-frontal tumour patients. Very few studies have investigated the presence and characteristics of anxiety in patients with primary brain tumours.

Very few studies have investigated the presence and characteristics of anxiety in patients with primary brain tumours. However, in a recent study, Arnold *et al* [22] reported 48% of their 363 patients with primary brain tumours had current generalized anxiety disorder according to the responses on the Modified Brief Patient Health Questionnaire. This rate of anxiety is concordant with the overall rate of anxiety of our combined frontal and non-frontal brain tumour patients which was 51.9%. Anxiety and depression have been found to be negatively associated with all aspects of quality of life [29]. The high rates of depression and anxiety in our patients with frontal brain tumours highlights the importance of assessing the presence of neuropsychiatric illness in patients with brain tumours. The routine use of screening instruments for depression and anxiety in patient with brain tumours would inform more effective detection and treatment intervention. The HADS has been considered to be a more accurate screening measure of depression in glioma as it minimises somatic symptoms [21].

The neurobehavioural changes following brain tumour reported by a substantial percentage of both relatives of and patients with brain tumours in our study highlight the need for support and management for relatives as much as patients. As personality change is one of the t factors associated with poor quality of life [5] and over 75% of the patients in our study have low-grade tumours and therefore relatively long survival potential treatment is particularly

important. Neurobehavioural changes are challenging for relatives, and not understanding the nature of these changes has been associated with more difficulty coping with them [30]. As a first step, information regarding potential neuorobehavioural changes including how to recognise, understand, predict and manage behaviours that are causing difficulties following brain tumour is likely to help both patients and their relatives "make sense" of these often challenging behaviours. In addition, better access to clinical neuropsychologists with expertise in cognitive impairment and neurobehavioural changes working within multidisciplinary neuro-oncology teams to provide support and to develop and implement coping strategies would help patients and their families manage the neurobehavioural sequelae of brain tumour and improve their quality of life.

There are several limitations to this study. First, the sample size is relatively small which restricts the extent to which the findings can be generalized. Second, given the small sample size and multiple analyses, there is an increased risk of type 1 error, although Hochberg corrections were applied to paired *t* test analyses to control for type 1 errors in multiple comparisons. Third, as this was an exploratory study with a relatively small sample, we did not attempt to investigate the relationship between a range of variables including type and grade of tumour, education level and potential treatment effects on behavioural changes. Future research with larger samples to establish whether particular variables are associated with greater neurobehavioural change in patients with brain tumour is required to inform care provision.

Summary

Little attention has been given to the neurobehavioural changes in patients with brain tumours. These results indicate that the subjective experience of a substantial proportion of patients with frontal tumours as well as patients with non-frontal brain tumours patients reaches *clinical* levels of difficulties with personality and behavioural changes, which impact on social functioning. The present study also reveals high rates of depression and anxiety in patients with primary brain tumours. Routine assessment of depression and anxiety will facilitate evidence-based management of depression and anxiety in patients with primary brain tumours and ultimately improve quality of life.

REFERENCES:

1. Adolphs R. The neurobiology of social cognition. *Curr Opin Neurobiol* 2001;**11**: 231–239.
2. Bar-On R, Tranel D, Denburg NL, et al. Exploring the neurological substrate of emotional and social intelligence. *Brain* 2003;**126**:1790-1800.
3. Lichter DG, Cummings JL. Introduction and overview. In: Lichter DG, Cummings JL, eds. Frontal-subcortical circuits in psychiatric and neurological disorders. New York 2001:1-43.
4. Stuss DT, Gallup GG, Alexander MP. The frontal lobes are necessary for 'theory of mind'. *Brain* 2001;**124**: 279-286.
5. Davies E, Clarke C. Views of bereaved relatives about quality of survival after radiotherapy for malignant cerebral glioma. *J Neurol Neurosur Psychiatr* 2005;**76**: 555-561.
6. Sterckx W, Coolbrandt A, Dierckx de Casterle B, et al. The impact of a high-grade glioma on everyday life: A systematic review from the patient's and caregiver's perspective. *Eur J Oncol Nurs* 2013;**17**:107-117.
7. Shandy-Ur T, Rankin KP. Personality and social cognition in neurodegenerative disease. *Curr Opin Neurol* 2011;**24**:550-555.
8. Barrash J, Tranel D, Anderson SW. Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. *Dev Neuropsychol* 2000;**18**: 355-381.
9. Hornak J, Bramham J, Rolls ET, et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulated cortices. *Brain* 2003;**126**:1691-1712.
10. Fleminger S. Head Injury. In: David A, Fleminger S, Kopelman MD, et al. eds. Lishman's Organic Psychiatry: A Textbook of Neuropsychiatry (4th Edition). Chichester: Blackwell Publishing, UK 2009:206.
11. Mah L, Arnold MC, Grafman J. Impairment of social perception associated with lesions of the prefrontal cortex. *Am J Psychiat* 2004;**161**:1247–1255.

12. Burgess PW. Strategy application disorder: The role of the frontal lobes in human multi-tasking. *Psychological Research* 2000;**63**:279-288.
13. Gilbert SJ, Burgess PW. Executive function. *Curr Biol* 2008;**18** (3):R110-R114.
14. Spiegel DR, Kim J, Greene K, et al. Apathy due to cerebrovascular accidents successfully treated with Methylphenidate: A case series. *J Neuropsychiatry Clin Neurosci* 2009;**21**:216-219.
15. Godbout L, Grenier MC, Braun CMJ, et al. Cognitive structure of executive deficits in patients with frontal lesions performing activities of daily living. *Brain Inj* 2005;**19** (5):337-348.
16. Andrewes DG, Kaye A, Murphy M, et al. Emotional and social dysfunction in patients following surgical treatment for brain tumour. *J Clin Neurosci* 2003;**10**(4):428-433.
17. Stuss DT, Gow CA, Hetherington CR. "No longer gage": Frontal lobe dysfunction and emotional changes. *J Consult Clin Psychol* 1992;**60** (3):349-359.
18. Grace J, Malloy PF. Frontal Systems Behaviour Scale. PAR Psychological Assessment Resources Inc. USA 2001.
19. Snaith RP, Zigmond AS. HADS: Hospital Anxiety and Depression Scale. GL Assessment, London, UK 1994.
20. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. *J Natl Cancer Inst* 2011;**103**:61-76.
21. Rooney AG, McNamara S, Mackinnon M, Frase M, et al. Screening for major depressive disorder in adults with cerebral glioma: an initial validation of 3 self-report instruments. *Neuro-Oncology* 2013;**15** (1):122-129.
22. Arnold SD, Forman LM, Brigidi BD, et al. Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumours. *Neuro-Oncology* 2008;**10**:171-181.
23. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;**75**: 800-803.

24. Stuss DT, Alexander MP. The anatomical basis of affective behaviour, emotion and self-awareness: A specific role of the right frontal lobe. In: Hatano G, Okada N, Tanabe H, eds. Affective Minds. The 13th Toyota Conference 2000;13-25.
25. Krueger CE, Laluz V, Rosen HJ, et al. Double dissociation in the anatomy of socioemotional disinhibition and executive functioning in dementia. *Neuropsychology* 2011;**25**(2): 249-259.
26. Beer JS, John OP, Scabini D, et al. Orbitofrontal cortex and social behaviour: Integrating self-monitoring and emotion-cognition interactions. *J Cogn Neurosci* 2006;**18**(6):871-879.
27. Gazzaley A, D'Esposito M. Unifying Prefrontal Cortex Function, Executive control, neural networks, and top-down modulation. In: Miller BL, Cummings JL, eds. The Human Frontal Lobe Functions and Disorders Second edition. The Guildford press New York 2007:187-206.
28. Wellisch DK, Kaleita TA, Freeman D, et al. Predicting major depression in brain tumour patients. *Psycho-Oncology* 2002;**11**:230-238.
29. Janda M, Steginga S, Langbecker D, et al. Quality of life among patients with a brain tumour and their carers. *J Psychosom Res* 2007;**63**(6): 617-623.
30. Schubart JR, Kinzie MB, Farace E (2008) Caring for the brain tumor patient: family caregiver burden and unmet needs. *Neuro-Oncology* 10:61-72