BRAIN COMMUNICATIONS

Subcortical contributions to higher cognitive function in tumour patients undergoing awake craniotomy

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Primary brain tumours often occur near eloquent regions, affecting language, motor and memory capacity, with awake mapping and tailored resection designed to preserve higher cognitive functioning. The effects of such tumours on subcortical structures, including the thalamus and basal ganglia, have been largely unexplored, in spite of the known importance of such structures to higher cognitive functioning. We sought to explore the effects of volume changes of subcortical structures on cognition, in 62 consecutive patients diagnosed with primary brain tumour and cavernous malformations, referred to our neurosurgical practice. We found right caudate to be highly predictive of intelligence, left pallidum of total neuropsychological function and right hippocampus of mood. Our study is the largest of its kind in exploring subcortical substrates of higher cognition in consecutive patients with brain tumours. This research supports prior literature, showing subcortical structures to be related to higher cognitive functioning, particularly measures of memory and executive functioning implicated in fronto-subcortical circuits. Furthermore, involvement of right mesial temporal structures in mood, further strengthens the central role of Papez circuit in emotional quality of cognition. Attention to subcortical integrity is likely to be important in discussing postsurgical cognitive outcome with patients and their families.
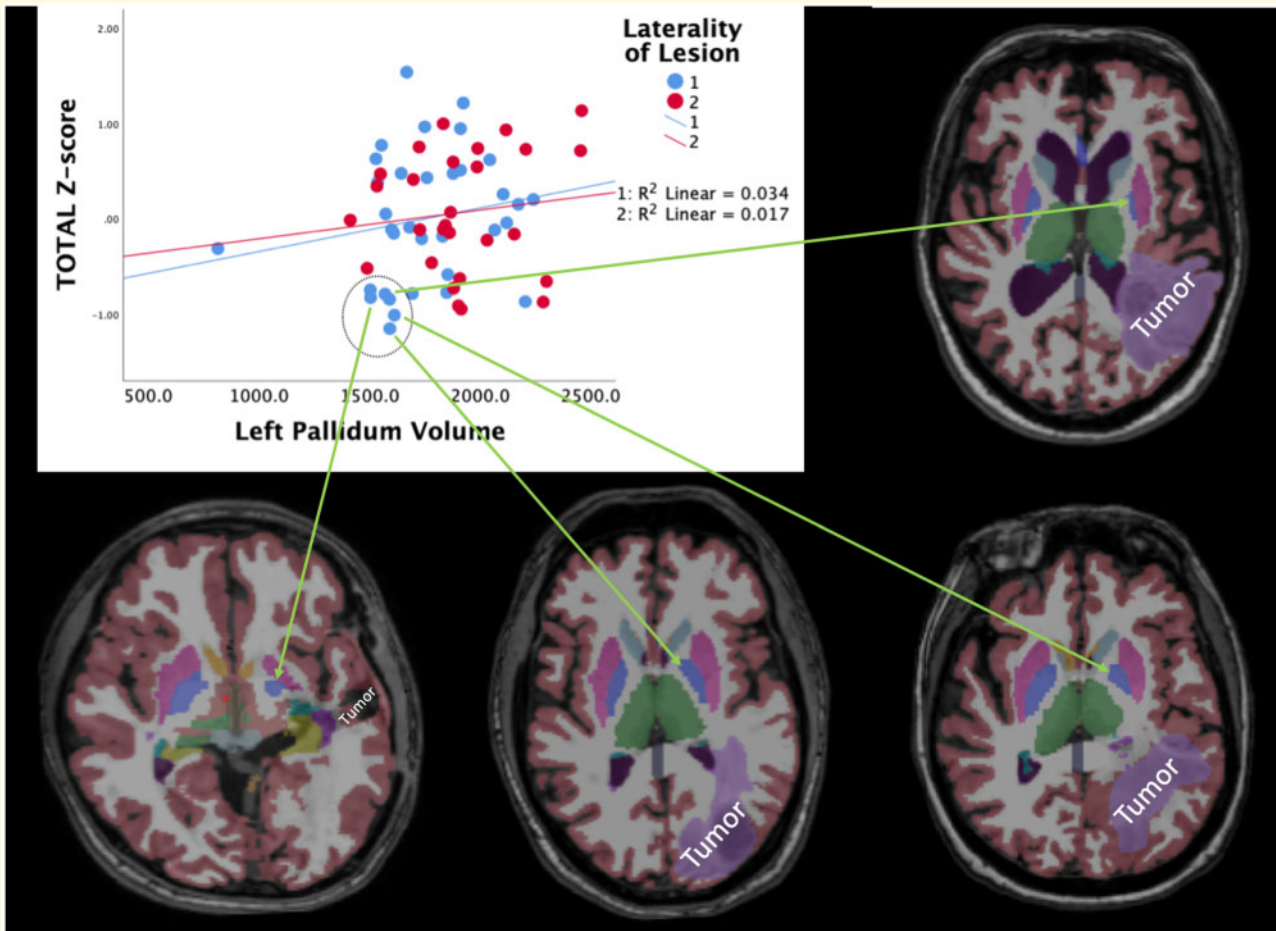
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Graphical Abstract

Introduction

The contributions of subcortical structures to higher cognitive function have been well described, with foundational studies involving patients with stroke (Hochstenbach *et al.*, 1998), Parkinson's disease (Rafal *et al.*, 1984) and dementia (Gold *et al.*, 2005). While early studies, using relatively gross techniques, found that number (but not volume) of subcortical infarcts was correlated with neuropsychological dysfunction (Corbett *et al.*, 1994), more sophisticated imaging techniques, including tracer studies in primates (Middleton and Strick, 2000), began to elucidate parallel frontal–subcortical 'loops' or 'circuits' underlying higher cognitive function, with three predominant circuits mediating motor, emotional and cognitive functioning (Cummings, 1993).

There are five main fronto-subcortical circuits, involving motor, oculomotor, executive, mood and motivational functioning (Cummings, 1993). Each of these share some common features: they originate in the prefrontal cortex, project to the striatum, then onto globus pallidus and thalamus and then link back to the prefrontal cortex.

Projections remain segregated as they pass through the caudate, lentiform nucleus and thalamus, suggesting functional organization (Mega and Cummings, 1994). Three circuits are of particular interest to human behaviour: *motor circuits* which originate within the supplementary, premotor, motor and somatosensory cortices, project to the putamen (in topographically organized manner), then to the globus pallidus, then substantia nigra, then thalamus, then back to cortex; the *dorsolateral prefrontal circuit* which originates in Broadmann Areas 9 and 10, projects to the dorsolateral head of the caudate, dorsomedial globus pallidus, substantia nigra, ventromedial and dorsomedial thalamus and back to dorsolateral prefrontal cortex; and finally, the *lateralorbitofrontal prefrontal circuit* originates in Broadmann Areas 10 and 11, then projects to ventromedial caudate, dorsomedial globus pallidus, substantia nigra, ventromedial and dorsomedial thalamus, then back to the cortex (Tekin and Cummings, 2002).

A recent meta-analysis of normal control subjects ($N = 3518$ participants; 45.3% female; age range 19–51), undergoing functional magnetic resonance imaging, was

undertaken (Arsalidou *et al.*, 2013). This study found that working memory processes (including encoding, storing, manipulating and retrieving), involved activations within bilateral anterior putamen and left lateral globus pallidus. Executive functioning (involving planning and task switching), was associated with activations within bilateral putamen, bilateral caudate body and the right caudate head. These authors noted that left putamen activation was more predominant for working memory tasks, implying more task verbalization, while the right caudate head was predominant for executive tasks, suggesting increased imaginability of task demands (Arsalidou *et al.*, 2013).

Remarkably few studies have endeavoured to assess volumetric associations between subcortical structures and higher cognitive functioning. In disease, basal ganglia atrophy has been associated with cognitive decline in multiple sclerosis (Batista *et al.*, 2012), preclinical Huntington's disease (Jurgens *et al.*, 2008) and amyotrophic lateral sclerosis (Machts *et al.*, 2015), with most showing caudate and putamen correlates with higher cognitive functioning. In a lesion mapping study of cognitive abilities associated with intelligence, including 16 with brain tumours, researchers found left caudate and putamen to be associated with verbal intellectual abilities (Verbal Comprehension Index) comprised of subtests including Vocabulary, Similarities and Information (Gläscher *et al.*, 2009). Even fewer studies have involved normal cohorts, with relatively consistent findings showing caudate volumes to be positively associated with intellectual functioning (Grazioplene *et al.*, 2015). Our group has demonstrated associations between various subcortical structures, including caudate, putamen, hippocampus and thalamus, and measures of aptitude (Jung *et al.*, 2014), creativity (Jung *et al.*, 2015) and imaginative ability (Jung *et al.*, 2016). Thus, volume measures of subcortical structures, including the basal ganglia and thalamus, predict higher cognitive functioning in both health and disease.

No studies, to date, have been exclusively undertaken to study subcortical contributions to higher cognitive abilities in patients with brain tumour. Primary brain tumour presents a compelling testbed for such an investigation given: (i) the broad distribution of tumours throughout the cerebral cortex, (ii) the variable growth trajectory of tumours affecting surrounding structures in either acute or chronic manner and (iii) the variable impact on subcortical structures through overt compression of structures and/or oedema/infiltration into projection tracts linking frontal–subcortical circuits. We hypothesized that the volume of subcortical structures would predict performance on a broad battery of cognitive tests in tumour patients, with previous literature informing our predictions that: (i) left putamen and pallidum volume would be predictive of measures sensitive to working memory and verbal functioning (e.g. encoding, storing, manipulating and retrieving) and (ii) right caudate volume would predict performance on executive functioning and imaginative tasks (e.g. planning and task switching).

Methods

Patient population

We identified 62 consecutive patients (35 men, mean age = 49 ± 17.5) who underwent planned awake resections of primary ($n = 55$, 88%) and metastatic ($n = 4$, 6%) brain tumours, and symptomatic cavernous malformations, a benign tumour of blood vessels ($n = 4$, 6%) at the University of New Mexico Hospital between 2015 and 2019. This study was approved by our institutional review board under study protocol #18-044. This study utilized chart review data obtained through routine clinical care, and waiver was obtained from the institutional review board for use of data for analysis.

Pre-operative neuropsychological evaluation

All 62 patients underwent pre-operative standard neuropsychological evaluation to assess baseline cognitive functioning and to determine patient's ability to undergo resection in an awake state. Patients were administered an extensive battery of tests including: Test of Memory Malingering; Test of Premorbid Functioning; Wechsler Abbreviated Scale of Intelligence 2nd Edition; Neuropsychological Assessment Battery Screening (NAB-Screening); NAB (NAB-Language, Spatial, Executive); Processing Speed Index – Wechsler Adult Intelligence Scale—IV (Processing Speed Index-WAIS-IV); Rey Complex Figure Test; Brief Visual Memory Test Revised; California Verbal Learning Test—II; Controlled Oral Word Association Test; Trail Making Tests—Parts A & B; Grip Strength; Grooved Pegboard Test; Clinical Assessment of Depression; Wisconsin Card Sort Test; Trauma Symptom Inventory – II.

Imaging

All patients underwent a pre-operative standard clinical scan which included functional magnetic resonance imaging, fluid-attenuated inversion recovery, T2 and T1 sequences. For our analysis, we focused only on the T1 sequences collected on a 3 T Phillips Ingenia scanner with the following acquisition parameters: echo time = 3.5 ms, repetition time = 7.9 ms, flip angle = 8°, voxel resolution = 0.9375 mm in plane, slice thickness = 1 mm. Three patients were scanned on a Siemens Symphony 1.5 T magnetic resonance imaging scanner: echo time = 4.68 ms, repetition time = 11 ms, flip angle = 20°, voxel resolution = 1 mm in plane, slice thickness = 1 mm. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer-v6.0 image analysis suite.

The methodology for FreeSurfer is described in full in several papers (Fischl *et al.*, 2002, 2004; Ségonne *et al.*, 2007). Briefly, this process includes automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Fischl *et al.*, 2002, 2004). Segmented data were then parcelled into units based on gyral and sulcal structure, resulting in values for cortical thickness, surface area and volume (Fischl *et al.*, 2004; Desikan *et al.*, 2006). Volume measures are a combination of thickness (a one-dimensional measure) and area (a two-dimensional measure) across 33 measures per hemisphere (i.e. 66 across the surface of the brain) as well as seven subcortical volumes per hemisphere (i.e. 14 across the brain) including bilateral caudate, putamen, globus pallidus, nucleus accumbens, thalamus, amygdala and hippocampus (Fischl *et al.*, 2002). All processed images were inspected for image quality. All tumour volumes were manually identified and masked by a neurosurgeon (M.C.) and re-processed to ensure accurate subcortical volumes.

Statistical analysis

Z-scores were created across three major neuropsychological domains including: Total Z-score, comprised of Attention, Memory, Language, Visuo-spatial and Executive functioning; Motor Z-score, comprised of grip strength in dominant and non-dominant hand, and grooved pegboard in dominant and non-dominant hand, and Mood Z-score, comprised of Total score on the Clinical Assessment of Depression. Mean and standard deviation scores were calculated across all subjects to derive Z-score transformations. Particular subtests for each domain are as follows: *Attention* – Trail Making Test Part A, NAB Digit Span Forward, NAB Visual Attention Part B Efficiency; *Memory* – Brief Visual Memory Test – Delayed Recall, California Verbal Learning Test – Delayed Recall; Rey Complex Figure Test – Delayed Recall; *Language* – Boston Naming Test, Vocabulary (Wechsler Abbreviated Scale of Intelligence), Controlled Oral Word Association Test Animal Naming; *Motor (Dominant)* – Grip Strength, Grooved Pegboard (Dominant Hand); *Motor (Non-Dominant)* – Grip Strength, Grooved Pegboard (Non-Dominant Hand); *Visuo-Spatial* – Rey Complex Figure Test Copy Trial, Block Design (Wechsler Abbreviated Scale of Intelligence), NAB Visual Designs; *Executive* – Trail Making Test Part B, Controlled Oral Word Association Test (FAS), NAB Digits Backward; Mood – Clinical Assessment of Depression total score.

Linear regression models were used to regress all subcortical volumes from both hemispheres (caudate, putamen, globus pallidus, thalamus, hippocampus and amygdala), against the Full Scale Intelligence Score, Total Z-score, Mood Z-score to determine the relationship between subcortical structures and broad cognitive/mood functioning. We controlled for age, sex and total segmented brain volume in each analysis. Family-wise P was held to $P < 0.05$ to control for Type I error given multiple comparisons. ANOVA was used to evaluate the relationship between lesions located within (or very near/compressing) the basal ganglia and performance on measures of intelligence, neuropsychological performance and mood. Tumours involving the basal ganglia were determined by the neurosurgeon (M.C.), who was blind to performance on cognitive and mood tasks, and coded as involving left basal ganglia ($N = 10$), right basal ganglia ($N = 7$) or neither basal ganglia ($N = 45$). *Post hoc* analysis (with Bonferroni correction) was carried out by group to determine significant group differences across more specific measures of intelligence (Block Design, Matrix Reasoning, Vocabulary, Similarities) and neuropsychological domain (Attention-Z, Language-Z, Memory-Z, Visuo-spatial-Z and Executive-Z, Motor-Dominant-Z, Motor-Non-Dominant-Z).

Data availability

Raw data (SPSS file) used for all analyses is available upon request.

Results

Clinical demographics are present in Table 1. Consistent with previous studies regarding intelligence, we found that the right caudate volume predicted Full Scale Intelligence Score across the sample ($F = 3.6$, $P = 0.01$, $r^2 = 0.20$, $\beta = 0.26$).

A model including both left pallidum and right caudate volume predicted Total Z-score across the entire sample ($F = 8.3$, $P < 0.001$, $r^2 = 0.43$, left pallidum $\beta = 0.28$; right caudate $\beta = 0.22$; Fig. 1).

For motor functioning, we found that a model including the right thalamus and right putamen predicted Motor Z-score ($F = 11.5$, $P < 0.001$, $r^2 = 0.53$, right thalamus $\beta = -0.45$, right putamen $\beta = 0.38$; Fig. 2). Finally, for mood functioning, we found that a model including the right hippocampus and left amygdala predicted Clinical Assessment of Depression score ($F = 2.6$, $P = 0.04$, $r^2 = 0.23$, right hippocampus $\beta = -0.40$, left amygdala $\beta = -0.32$).

For subjects with low left pallidum values and low Total Z-scores (circled in dashed black line on Fig. 2),

**Table 1 Clinical and demographic characteristics of sample**

| Tumour type	N	Age (SD)	Male sex, n (%)	Full Scale Intelligence Score
Primary	54	49.8 (17.3)	33 (60%)	93.3 (16.1)
Metastatic	4	50.5 (17.4)	1 (25%)	94.0 (13.5)
Cavernoma	4	37 (19.9)	1 (25%)	85.5 (7.3)
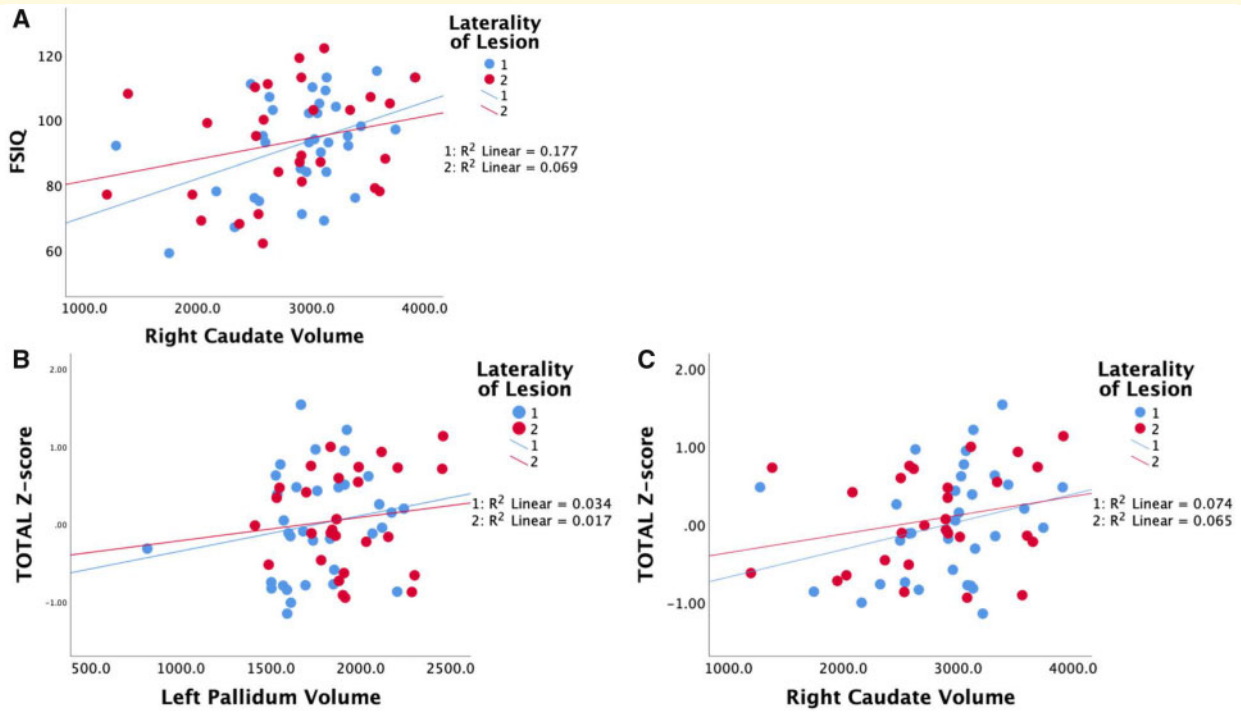
Figure 1 Relationship between right caudate volume and Total Z-score. (**A**) Scatterplot of Full Scale Intelligence Score – Right Caudate Volume Relationship. (**B**) Scatterplot of Total Z-score – Left Pallidum Volume Relationship; (**C**) Scatterplot of Total Z-score – Right Caudate Volume Relationship (Blue = Left Hemisphere; Red = Right Hemisphere).
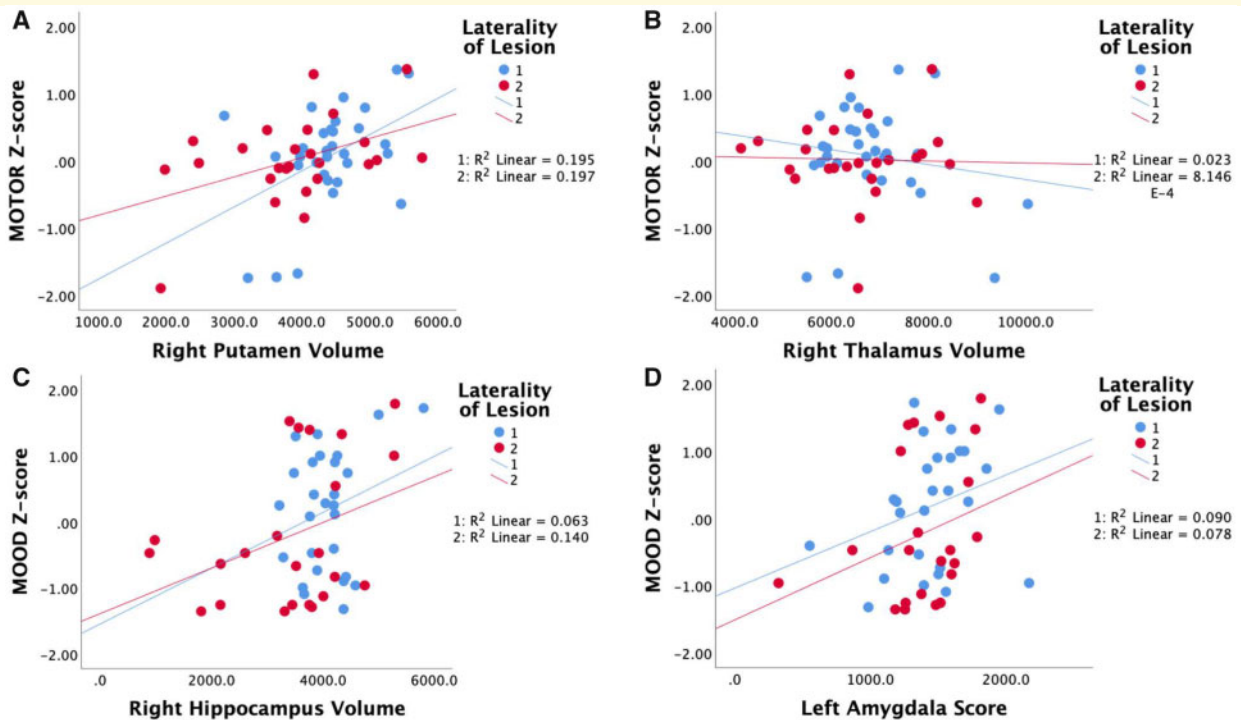
Figure 2 Relationship between right putamen and Motor Z-score. (**A**) Scatterplot of Motor Z-score – Right Putamen Volume Relationship; (**B**) Scatterplot of Motor Z-score – Right Thalamus Relationship. (**C**) Scatterplot of Mood Z-score – Right Hippocampus Volume Relationship; (**D**) Scatterplot of Mood Z-score – Left Amygdala Volume Relationship. (Blue = Left Hemisphere; Red = Right Hemisphere).
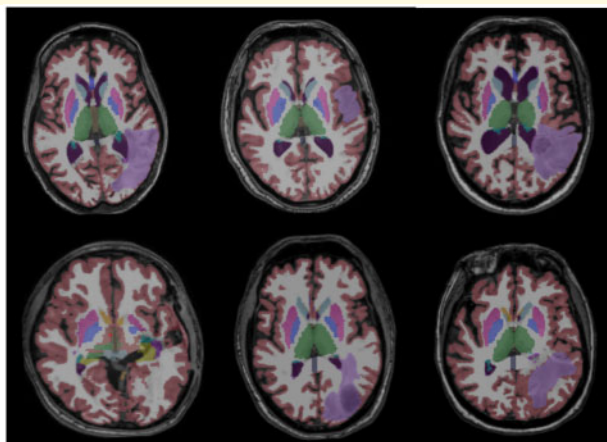
Figure 3 Segmented volumes of subcortical regions and tumour in six patients with left hemispheric lesions (radiological convention) and lowest Total Z-scores.
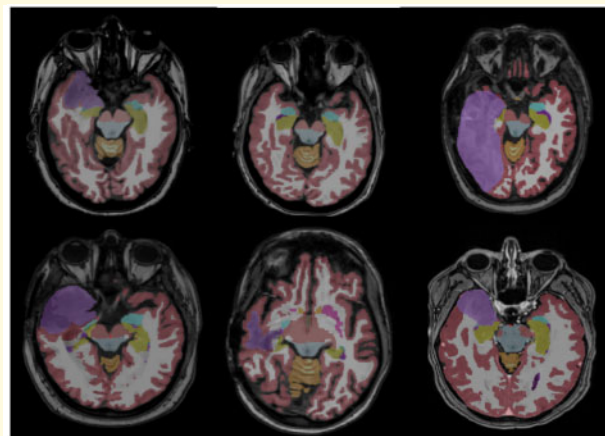
Figure 4 Segmented volumes of subcortical regions and tumour in six patients with right hemispheric lesions (radiological convention) and lowest Mood Z-scores.

we were interested whether the tumour was compressing the structures within the left hemisphere, leading to reduced subcortical volumes. To illustrate this concept, we present segmented volumes of subcortical regions and tumour in six patients with left hemispheric lesions and very low Total Z-scores (Fig. 3). Comparing left (radiological convention) to right globus pallidus volumes within these six patients, it is evident that volumes are significantly reduced/compressed within the hemisphere affected by the tumour.

Similarly, we illustrate the effect of right hippocampus volume, on Mood Z-score (Fig. 4). As depicted, adverse score on mood was related to right hemisphere tumour, and compression/infiltration of tumour or oedema into regions within and surrounding the right hippocampus. Again, it is evident that compression of mesial temporal lobe structures, particularly the hippocampus (yellow), affects volume in right tumour patients, when compared to the contralateral side.

Finally, to evaluate more formally the relationship between tumour involvement of the basal ganglia and cognitive performance, we compared patients with lesions involving the left basal ganglia ($N = 10$), lesions involving the right basal ganglia ($N = 7$) and lesions involving neither basal ganglia ($N = 45$) across measures of intellectual functioning and mood. We found that, on gross measures of cognitive and intellectual functioning, patients did not differ across measures of intelligence ($F = 1.6$, $P = 0.21$), Total Z-score ($F = 0.94$, $P = 0.39$) or Motor Z-score ($F = 1.97$, $P = 0.15$). However, on submeasures of intelligence (Block Design), significant group differences were observed ($F = 4.99$, $P = 0.01$), with patients having right basal ganglia lesions (Mean = 19.7, SD = 13.4) scoring significantly lower ($P = 0.008$) than patients with left basal ganglia lesions (Mean = 41.40, SD = 12.2), and patients with no basal ganglia lesions being intermediate

(Mean = 30.41, SD = 14.5). Similarly, while no group differences were observed across Total Z-score, group differences were observed across Spatial-Z, with right basal ganglia patients being significantly below left basal ganglia patients ($P = 0.002$), and both left ($P = 0.076$), and right ($P = 0.066$) basal ganglia patients being significantly lower than patients without basal ganglia lesions.

Discussion

This study represents the first attempt to link subcortical volumes to higher cognitive functioning in a consecutive cohort of tumour patients selected to undergo awake surgery and resection. Consistent with prior literature, we found positive relationships between right caudate volume and intelligence across our patient sample (Grazioplene et al., 2015). Also consistent with prior literature, we found positive relationships between left pallidum volume (as well as right caudate) and Total Z-score, with indication that compression of the left pallidum in select patients resulted in significant reductions across measures of global neuropsychological functioning, analogous to literature suggesting selective neuropsychological decline in lesions to this structure (Scott et al., 2002). Motor functioning was associated with volume of the right thalamus and right putamen, both of which are well associated with voluntary movement (Kimura et al., 1993). Finally, we found that mood functioning was predicted by volume of the right hippocampus and left amygdala, conforming to hypotheses linking the Papez circuit to depressive symptoms (Eggers, 2012), and consistent with research showing lower hippocampal volumes to be associated with major depression (Bremner et al., 2000). Tumour compression upon structures within the left pallidum and right hippocampus appear to constrain the

relationship at the low end of cognitive and mood functioning (respectively), likely modulating existing structure–function relationships involved in healthy brain-behaviour functioning.

Most relationships conformed to expectations given previous findings relating subcortical structures to higher cognitive functioning (Cummings, 1993; Tekin and Cummings, 2002), including in normal cohorts (Jung et al., 2014; Grazioplene et al., 2015). However, as we also included measures within the temporal lobe (i.e. hippocampus and amygdala), an unanticipated structure–function relationship emerged for mood. Previous research has noted the importance of hippocampal volume and mood, with volume of the right hippocampus being related with major depressive disorder (Sheline et al., 1996; Janssen et al., 2007), consistent with studies showing inverse relationships between hippocampal volume and duration of illness (Lampe et al., 2003). While hypotheses regarding fronto-subcortical loops would predict that caudate nucleus volume changes would be associated with symptoms of depression (Tekin and Cummings, 2002), our results suggest that the hippocampus predominates, supporting the importance of the Papez circuit in mood functioning in health and disease (Papez, 1937). This circuit originates in the hippocampus, traverses the fornix and mammillary bodies, continues to the anterior nucleus of the thalamus, connecting anterior cingulum via thalamic radiations, and circling around the corpus callosum and back to the entorhinal cortex, terminating back at the hippocampus (Shah et al., 2012). Our findings add the Papez circuit, critical to normal mood functioning, to the broad theoretical framework provided by fronto-subcortical circuits, in understanding the broad spectrum of higher cognitive and emotional functioning in humans.

This research was the first to be undertaken exclusively with patients suffering from tumours of the brain, which disrupt the structure and function of surrounding brain structures, including basal ganglia, thalamus and mesial temporal lobe grey matter structures (i.e. hippocampus and amygdala). This focus allows for more refined understanding of the effects of local 'stressors' on subcortical structures in the absence of overt lesions caused by stroke and traumatic injury, which often ablate the structures themselves, as well as alter the connectivity between them and other structures within cortico-subcortical loops. This approach increased the understanding regarding structure–function relationships between important subcortical structures, which remain viable within functional loops, but which are under increasing pressure given tumour growth, surrounding oedema, and other metabolic abnormalities associated with tumour progression. Our results appear to reflect heightened structure–function effects, with patients having local tumours that compress structures related to a particular function (i.e. Total Z-score and depression), being observed to have a higher prevalence of reduced functional capacity. Our results appear to show more pronounced deficits in patients where tumours involve the right basal ganglia, affecting more specific measures of non-verbal intellectual functioning (i.e. Block Design) and visuo-spatial functioning (e.g. Spatial Z). These results support more specific structure–function relationships between more lateralized fronto-subcortical networks, in this case involving non-verbal intellectual and cognitive functioning, and localized disruption due to tumour presence and progression. Future work will be necessary to determine if reduction of structural pressure associated with brain tumours, following surgical resection, results in recovery of function and associated increase in subcortical volumes.

Our study has several weaknesses, which future studies should address. We have only included imaging and neuropsychological correlates for patients at baseline, given common imaging parameters and neuropsychological measures being administered at that time. Most patients underwent chemotherapy and radiation treatment following surgical resection, both of which have further effects on neuropsychological functioning and brain structure (Kesler et al., 2013; McDonald et al., 2013; Jacob et al., 2018). However, longitudinal measures assessing possible structural and functional changes over time, with neuroimaging would help to determine whether structure–function relationships change following removal of the tumour hypothesized to constrain such relationships in affected patients.

Competing interests

The authors report no competing interests.

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