LONG-TERM SPEECH AND LANGUAGE DEFICITS AND ASSOCIATED NEURAL CORRELATES IN SURVIVORS OF PAEDIATRIC POSTERIOR FOSSA TUMOURS

Olha Hodgson BSc, MSc

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Abstract (short)

Background: The present research is the first multi-modal study of language deficits in long-term PFT survivors to date. In addition to a detailed neuropsychological assessment of language, this thesis investigated neural correlates of language processing by employing functional (fMRI) and diffusion (DTI) magnetic resonance imaging techniques.

Method: Twenty-one PFT survivors, aged 16-21, and twenty-two matched healthy volunteers completed a series of neuropsychological assessments, task-based language fMRI study (targeting semantic retrieval and speech articulation), and a DTI study. The patients’ clinical profiles and oro-motor functioning were also analysed.

Results: Patients demonstrated significantly poorer performance in semantic content, expressive and receptive skills, verbal memory, reading and writing, visuo-motor coordination and non-verbal intelligence, with elevated internal variability of the linguistic profiles, when compared to controls. Semantically-related language skills contributed more to the between-group differences than non-verbal cognitive skills. A significant association between language and non-verbal cognitive abilities in both patients and controls was unconfounded by the age and disease.

On fMRI, patients lacked metabolic response in the pre-central and post-central gyri during semantic retrieval. Broca’s, Wernike’s and Geschwind’s areas responded similarly in both hemispheres, with no significant differences between the groups. In all participants Language Content Index predicted the BOLD
response on the border of the left lateral occipital cortex and angular gyrus. Expressive Language Index predicted BOLD response in the right frontal pole, paracingulate gyrus, superior frontal gyrus, and middle frontal gyrus. In healthy controls, articulation of speech was associated with activation in the Crus I and Crus II of the right cerebellar hemisphere. Semantic load triggered activation in the Crus VI and VIIb of the vermis, as well as right lobules V and VI of the cerebellum.

DTI revealed a global decrease in the fractional anisotropy and increase in the diffusivity scalars in patients, compared to controls, but not different between those patients that received and did not receive radiotherapy. Patients also demonstrated significant reduction in FA index in the bilateral arcuate fasciculus and increased diffusivity in the bilateral SCP. The FA index in the segments of the left-hemispheric cortico-spinal tract, anterior thalamic radiation, superior longitudinal fasciculus and inferior fronto-occipital fasciculus, positively predicted Language Content Index score in patients.

Clinical profiles analysis indicated that younger age at diagnosis, radiotherapy treatment and longer duration of mutism (if present) were associated with the poorest language outcomes. Patients with the longest recovery time demonstrated the best manual dexterity abilities. 38% of the patients that met the criteria for a diagnosable language disorder also had reduced oro-motor functioning and reduced FA within left arcuate fasciculus, compared to the remaining patients.

Conclusions. Despite the fact that PFTs do not directly impact cortical language-associated areas, patients, particularly those
treated with radiotherapy at a younger age, demonstrate deficits in all aspects of language processing. Semantic processing difficulties in PFT survivors are underpinned by the diminished cortical metabolic response during associated task performance, and microstructural changes in the left-hemispheric white matter. Tumours affecting the right cerebellar hemisphere may further predispose patients to developing difficulties in accessing language semantics.
Abstract (short)
Abstract (detailed)

Background
Language is a key function underpinning social adaptation and academic success. The growing body of research on the role of the cerebellum in language processing (Marien et al., 2014) has indicated that posterior fossa tumour (PFT) patients may be at risk of developing language deficits. So far, a limited number of studies have investigated this topic, and the findings are mixed, relying only on behavioural evidence. The present research is the most comprehensive, multi-modal study of language deficits in long-term PFT survivors to date. In addition to the detailed neuropsychological assessment of language, the study also investigated neural correlates of language processing by employing functional (fMRI) and diffusion (DTI) magnetic resonance imaging techniques, previously not utilised in the PFT population for this purpose.

Method
Design. An analytic observational approach was adopted as an overarching methodology. A cohort design was followed as it is best suited to a comparative analysis of language deficits as an outcome of interest in PFT-exposed and non-exposed groups (Song & Chung, 2010).
Participants. Twenty-one patients, surgically treated for any type of PFT before their 16th birthday, between 1994 and 2014 at the Nottingham University Hospitals, UK, were identified by accessing hospital records. All of the patients were aged between 16 and 22 years at the time of the assessment. Twenty-two healthy volunteers were recruited from the local community, and group-matched to the clinical group by age, gender and socio-
economic background. All participants completed neuropsychological assessments; sixteen patients and twenty healthy volunteers took part in the functional MRI study; fifteen patients and nineteen healthy volunteers took part in the DTI study.

Procedure. Participants underwent a detailed assessment of their language abilities, using the Clinical Evaluation of Language Fundamental, 5\textsuperscript{th} edition, test battery, an assessment of their non-verbal cognitive skills, using Raven’s Progressive Matrices Plus edition, and an assessment of their visuo-motor coordination, using the Purdue Pegboard test. For the PFT patients, their oro-motor abilities were also assessed using the Frenchay Dysarthria Assessment, 2\textsuperscript{nd} edition. The cortical metabolic response during language processing was examined using task-based functional MRI. The structural integrity of the white matter was evaluated using diffusion MRI. Finally, the patients’ clinical profiles were analysed in relation to the observed functional outcomes.

Results

Neuropsychological assessment. On the language assessment, the patients as a group performed significantly less well than the controls, although still within the normal range. All of the assessed language areas were impacted, including semantic content, expressive and receptive skills, verbal memory, reading and writing. Deficits were also observed in the non-linguistic functional domains: visuo-motor coordination and non-verbal cognitive abilities. MANOVA and discriminant function analysis revealed that language skills, which are reliant on access to semantic content, contributed more to the between-group
differences than non-verbal cognitive skills. A Pearson’s
correlational analysis revealed a significant association between
language and non-verbal cognitive abilities. The strength of this
association, as assessed by a Fisher’s z-transformation,
remained stable for both groups. A bivariate and partial
correlation model comparison indicated that the correlation was
not confounded by the age at assessment or group belonging.
The coefficient of variation analysis indicated that patients’
linguistic profiles were significantly less uniform, with a larger
discrepancy between the lowest and highest scores on the
individual language tests, compared to the healthy controls.

*Functional MRI.* Between-group contrasting of the cortical
activation patterns indicated that the patients lacked metabolic
response in the pre-central and post-central gyri during semantic
retrieval. A mixed ANOVA revealed that the regions of interest,
positioned within the classical perisylvian language-associated
network (Broca’s, Wernike’s and Geschwind’s areas), responded
similarly in both hemispheres, with no significant differences
between the groups. A regression analysis, controlling for the
effect of non-verbal IQ performance, indicated that overt
semantic processing predicts the response in the left
hemisphere, on the border of the lateral occipital cortex and
angular gyrus. At the same time, overt expressive language
performance predicted the response in the right hemisphere: the
frontal pole, paracingulate gyrus, superior frontal gyrus, and
middle frontal gyrus. Analyses of the cerebellar activation were
performed in the healthy controls and revealed that articulation
of speech is associated with activation in the Crus I and Crus II
of the right cerebellar hemisphere; while Semantic retrieval was
associated with activation in the Crus VI and VIIb of the vermis, as well as right lobules V and VI.

**Diffusion MRI.** The tract-based spatial statistics method (TBSS) was applied to demonstrate global deterioration of the white matter quality in PFT survivors, evident from the widespread decrease in the fractional anisotropy (FA) index, as well as the global increase in the mean (MD), axial (AD) and radial (RD) diffusivities. Diffusion scalar values, extracted from the bilateral arcuate fasciculi (AF) and superior cerebellar peduncles (SCP), demonstrated a reduced FA index in the bilateral AF and increased MR, RD and AD in the bilateral SCP in the patients. No significant correlations were observed between FA, MD, RD or AD in any of the ROIs and CELF-5 index scores. No significant differences in the WM microstructure were found between the radiotherapy-treated and non-treated groups of patients. The FA index in the segments of the left-hemispheric cortico-spinal tract, anterior thalamic radiation, superior longitudinal fasciculus and inferior fronto-occipital fasciculus, positively predicted performance on the measure of linguistic semantic access in the patients.

**Clinical profiles.** Exploratory two-step cluster analysis and post-hoc Pearson’s correlational analysis revealed younger age at diagnosis is associated with diminished language skills only in radiotherapy-treated patients but not in those that did not receive adjuvant radiotherapy. 38% of the patients met the CELF-5 criteria for a diagnosable language disorder (LD). These patients were also characterised by significantly reduced oro-motor reflexes control and intelligibility of speech, compared to
the remaining patients. There was no difference in the amount of the above-threshold activation during fMRI task between LD and non-LD patients. On DTI, LD patients have demonstrated reduced FA index compared to non-LD patients within the left arcuate fasciculus. Among three patients with a history of cerebellar mutism, the poorest language outcomes (but not cognitive outcomes) were observed in a patient with the longest duration of mutism.

**Conclusions**

Despite the fact that PFTs do not directly impact cortical language-associated areas, patients, particularly those treated with radiotherapy at a younger age, demonstrate deficits in all aspects of language processing. Semantic processing difficulties in PFT survivors are underpinned by the diminished cortical metabolic response during associated task performance, and microstructural changes in the left-hemispheric white matter. Tumours affecting the right cerebellar hemisphere may further predispose patients to developing difficulties in accessing language semantics. Future imaging studies should investigate the metabolic signatures of other language functions, beyond those explored in the present research. Investigations of the post-PFT white matter changes, associated with language deficits, would benefit from the application of more individualised approaches such as white matter tractography. Further patient-focused research is also required, concerned with the development of individualised rehabilitation approaches that incorporate language training.
Conference presentations


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<th>Explanation</th>
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<tbody>
<tr>
<td>4thV</td>
<td>Fourth Ventricle</td>
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<tr>
<td>AC</td>
<td>Asrocytoma</td>
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<tr>
<td>AD</td>
<td>Axial Diffusivity</td>
</tr>
<tr>
<td>AF</td>
<td>Arcuate Fasciculus</td>
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<tr>
<td>AIC</td>
<td>Akaike's Information Criterion</td>
</tr>
<tr>
<td>BA</td>
<td>Broca's Area</td>
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<tr>
<td>BET</td>
<td>Brain Extraction Tool</td>
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<tr>
<td>BS</td>
<td>Brainstem</td>
</tr>
<tr>
<td>C</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>CBTRC</td>
<td>Children's Brain Tumour Research Centre</td>
</tr>
<tr>
<td>CCAS</td>
<td>Cerebellar Cognitive Affective Syndrome</td>
</tr>
<tr>
<td>CELF-5</td>
<td>Clinical Evaluation of Language Fundamentals, 5th edition</td>
</tr>
<tr>
<td>ChT</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>CLS</td>
<td>Core Language Score</td>
</tr>
<tr>
<td>CM</td>
<td>Cerebellar Mutism</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebro-Spinal Fluid</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>DIPG</td>
<td>Diffuse Intrinsic Pontine Glioma</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
</tr>
<tr>
<td>ELI</td>
<td>Expressive Language Index</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo Planar Imaging</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>FDA-2</td>
<td>Frenchay Dysarthria Assessment, 2nd edition</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FSL</td>
<td>FMRIB Software Library</td>
</tr>
<tr>
<td>GA</td>
<td>Geschwind's Area</td>
</tr>
<tr>
<td>GM</td>
<td>Grey Matter</td>
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<tr>
<td>GUI</td>
<td>Graphic User Interface</td>
</tr>
<tr>
<td>HGG</td>
<td>High Grade Glioma</td>
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</tbody>
</table>
List of abbreviations

LCI - Language Content Index
LD - Language Disorder
LMI - Language Memory Index
M - Mean
MB - Medulloblastoma
MD - Mean Diffusivity
Mdn - median
MNI - Montreal Neurological Institute
MRI - Magnetic Resonance Imaging
MSA - Mutism and Subsequent Dysarthria
NAA - N-acetylaspartate
NHS - National Health Service
NMR - Nuclear Magnetic Resonance
NUH - Nottingham University Hospitals
PET - Positron Emission Tomography
PFS - Posterior Fossa Syndrome
PFT - Posterior Fossa Tumour
PPB - Purdue Pegboard
QOL - Quality of Life
RCT - Randomised Controlled Trial
RD - Radial Diffusivity
RF - Radiofrequency
RLI - Receptive Language Index
RPM - Raven's Progressive Matrices
RT - Radiotherapy
SALT - Speech and Language Therapist
SCP - Superior Cerebellar Peduncle
SD - Standard Deviation
SEM - Standard Error of the Mean
SLI - Specific Language Impairment
TBSS - Tract-Based Spatial Statistics
VBM - Voxel-Based Morphometry
List of abbreviations

WA - Wernicke's Area
List of abbreviations
Chapter 1: Introduction to the study

Key points

- Tumours of the posterior cranial fossa (PFTs) are the most common type of paediatric brain tumours;
- Structures affected by PFTs include the cerebellum, the brainstem and the fourth ventricle;
- Known complications of PFT treatment include cognitive deficits and motor deficits, socio-emotional deficits and reduced quality of life; these domains are typically examined using observations, neuropsychological assessments, and self-reports;
- The long-term impact of PFTs on language abilities is still debated, despite the growing awareness of the involvement of the cerebellum in the modulation of language;
- Magnetic resonance imaging provides a means of non-invasively investigating the functional and structural changes in PFT patients’ brains that may underpin overt behavioural changes;
- An observational study is proposed that will combine behavioural and MRI methods in order to offer a novel angle of evidence on the long-term language deficits in PFT survivors.

1.1 Posterior fossa tumours in childhood

Brain and other CNS tumours remain the biggest cause of childhood cancer-related deaths, despite the fact that cancer survival rates have increased significantly in recent decades (Cancer Research UK, 2017). Around 500 children are diagnosed with a brain tumour each year in the UK, and approximately 60% of these arise in the posterior fossa (The Brain Tumour Charity, 2016a). Alongside the constantly
improving standards or care and treatment of these tumours, a growing challenge is ensuring that surviving children enter adulthood with minimal functional deficits that may prevent them from leading healthy, socially engaged and fulfilling lives.

1.1.1 Anatomy of the posterior cranial fossa

The posterior cranial fossa is comprised of the cerebellum and segments of the brainstem, including the pons and the medulla oblongata. The posterior fossa structures are separated from the cerebrum by the dural sheet, the tentorium cerebelli. For this reason, PFTs are also commonly referred to as ‘infratentorial’ tumours, while the neoplasms arising above the tentorium are termed ‘supratentorial’. The fourth ventricle is the cavity filled with cerebro-spinal fluid (CSF) that lies between the cerebellum on the one side, and the pons and medulla on the other side. The ventricle itself is lined by ependymal cells where tumours can also arise (Figure 1.1).

![Figure 1.1. Key structures of the posterior cranial fossa. From (Gupta & Summors, 2001).](image_url)
The cerebellum (from the Latin ‘little brain’) is the hind brain structure, comprised of the two cerebellar hemispheres and the vermis, a midline narrow structure connecting the hemispheres. Similar to the cerebral cortex, the surface of the cerebellum is greatly increased by extensive folding, with elevations (folia) and grooves (sulci). Medio-laterally, the cerebellum can also be sub-divided into the anterior lobe (lobules I – V), the posterior lobe (lobules VI – IX), and the flocculonodular lobe (lobule X), (Figure 1.2.).

Grey matter is found in the cerebellar cortex and in the deep cerebellar nuclei, positioned within the white matter. These include the dentate, emboliform, globose and fastigial nuclei (Figure 1.3). Axonal projections, connecting the cerebellum with the rest of the CNS, pass through the three pairs of the cerebellar peduncles (inferior, middle and superior). The middle cerebellar peduncle is the largest out of these, and predominantly contains afferent fibers, which relay signals from the cerebral cortex to the cerebellum, via the pontine nuclei. The inferior cerebellar peduncle is composed of both afferent and efferent projections. Finally, the superior
cerebellar peduncle mainly contains efferent fibers, originating from the dentate, interposed and fastigial nuclei, which carry signals from the cerebellum via the thalamus to the cerebral cortex (Minagar, 2014).

*Figure 1.3. Deep cerebellar nuclei. From (Patestas & Gartner, 2016)*

Functionally, the cerebellum is sub-divided into the vestibulocerebellum (involved in vestibular reflexes and posture maintenance), the spino-cerebellum (involved in integration of sensory input and motor coordination), and the cerebro-cerebellum (involved in the planning and timing of movement, and cognitive function). The cerebro-cerebellum, also referred to as the neocerebellum, is particularly relevant to the investigation of cognitive and linguistic deficits, occurring as a result of cerebellar damage. The key structures of the cerebro-cerebellum are the lateral cerebellar hemispheres and the dentate nucleus. Current functional neuroimaging evidence from task-based activation studies suggests that non-motor linguistic function is localised to the ventrocaudal part of the dentate nucleus and lobules VI – VIII of the right posterior-lateral cerebellum (Marien et al., 2014); executive function is related to the activation of the Crus I and VIIB, and verbal working memory is linked to the activation of lobule VI and Crus I (Stoodley & Schmahmann, 2009). The involvement of the cerebro-cerebellum in higher order linguistic and cognitive
functions is thought to be facilitated by the cerebro-cerebellar WM loop, comprised of the afferent dentate-thalamo-cortical and efferent cerebro-ponto-cerebellar projections (Figure 1.4.), also discussed in Chapter 5 of the present thesis.

*Figure 1.4.* Schematic illustration of the core components of the cerebro-cerebellar loop. Corticospinal projections (A) carry information from the cerebral cortex to the ventral pons. The axons of the pontine neurons (B) further convey the signal to the cerebellar cortex. The dentate nucleus (DCN) receives signals via the cerebellar corticonuclear projections (C). The DCN sends projections to the thalamus (D) via the red nucleus. The circuit is completed by the thalamic projections (E), which reach the association cortices. From (Schmahmann, 1996).

### 1.1.2 PFT classification and treatment

There are two major classes of paediatric PFTs: primitive neuroectodermal tumours (PNETs) and glial tumours (Rasalkar, Chu, Paunipagar, Cheng, & Li, 2013). PNETs are highly malignant tumours that account for approximately a third of all PFTs in childhood, with the most common type being medulloblastomas. The term ‘PNET’ has been removed from the new brain tumour classification by the World Health
Organisation (WHO), issued in 2016, and these tumours are now referred to as ‘embryonal’ (Banan & Hartman, 2017). In regard to glial tumours, three sub-classes are differentiated: pilocytic astrocytomas, ependymomas and brainstem gliomas (Figure 1.5).

![Classification of the most common paediatric posterior fossa tumours](image)

**Figure 1.5. Classification of the most common paediatric posterior fossa tumours**

### 1.1.2.1 Medulloblastoma

Medulloblastomas are the most common type of malignant (cancerous) childhood brain tumours, which are more frequently diagnosed in boys (Rasalkar et al., 2013). The WHO 2016 guidelines recommend two strategies for the classification of medulloblastomas: histological and genetic. While histological classification is based on the morphological features of the tissue specimens, genetic classification is achieved by gene expression profiling or whole-genome methylation analysis (Louis et al., 2016; Banan & Hartmann, 2017). Regardless of the type, all medulloblastomas have been assigned the highest grade IV, meaning that they have a poorer prognosis compared with lower-grade tumours, and may require more aggressive treatment.
Most medulloblastomas arise sporadically in the cerebellum, and up to 75% of patients are diagnosed in the first decade of life. The tumour growth may restrict movement of the CSF in the fourth ventricle, leading to the obstructive hydrocephalus. For this reason, on clinical presentation, children with medulloblastomas may display cerebellar (poor balance, ataxia, dizziness) and hydrocephalic (nausea, vomiting, headaches) signs (Rasalkar et al., 2013). Medulloblastoma treatment typically involves a combination of surgery, cranio-spinal irradiation with a boost to the primary tumour bed, and chemotherapy. In patients under the age of three, radiotherapy is typically delayed, as it poses a high risk to the developing brain and may lead to long-term cognitive impairments (Barlett, Kortmann, & Saran, 2013).

1.1.2.2 Pilocytic astrocytoma

Astrocytomas are a sub-type of glial tumours that can arise anywhere in the brain, including the posterior fossa regions, within the cerebellum and brainstem (Bornhorst, Frappaz, & Packer, 2016). These are the most common paediatric brain tumours (malignant and non-malignant). Cerebellar pilocytic astrocytoma is a sub-type of glial tumour; it has been assigned Grade I by the WHO 2016 guidance due to its benign nature and slow growth rate. Pilocytic astrocytoma occurrence is not tied to any age-related pattern, but is more common in the first 10 years of a child’s life. The tumour is typically well-circumscribed with no metastases, which aids complete resection and improves the long-term prognosis (Rasalkar et al., 2013).

Due to the slow development of this type of tumour, symptoms may not become apparent until 3-6 months prior to the diagnosis. At the time of clinical evaluation, cerebellar
pilocytic astrocytoma patients typically show signs of cerebellar dysfunction and hydrocephalus-induced intracranial pressure (Bornhurst et al., 2016). The treatment for pilocytic astrocytoma is usually surgical with complete or near-complete resection. In the event of residual tumour progression, irradiation and/or chemotherapy may be used (Ogiwara, Bowman, & Tomita, 2012).

1.1.2.3 Ependymoma

Ependymomas are the third most common type of paediatric brain tumour after astrocytomas and medulloblastomas, arising from the ependymal cells of the ventricular system lining (Rasalkar et al., 2013). Consequently, CSF circulation is likely to be restricted, as the tumour increases in size, leading to hydrocephalus. Currently, the precise classification of ependymomas is unclear due to their molecular heterogeneity. Ongoing histological studies aim to provide more precise differentiation of the ependymoma sub-types in the future (Louis et al., 2016).

The standard treatment for paediatric ependymomas is surgery, followed by adjuvant radiotherapy. However, near-complete resection can only be achieved in 50-70% of cases (Rasalkar et al., 2012). Chemotherapy is sometimes used, but has not been reliably proven to improve outcomes or survival (Lin & Chintagumpala, 2015).

1.1.2.4 Brainstem glioma

Paediatric brainstem gliomas can arise from the midbrain, pons or medulla. The brainstem is involved in the regulation of vital body functions, including breathing, digestion and blood pressure, which makes these tumours particularly dangerous. Typically, these tumours are diagnosed in children
between the ages of 5 and 9 (Walker, Punt, & Sokal, 2004). The precise location of the brainstem glioma determines the clinical symptoms, which may include double vision, peripheral facial nerve palsy, extremity weakness, ataxia, and the Babinsky sign (elevation of the toe on stimulation, a sign the upper motor neuron dysfunction (Miller & Johnston, 2005)). Hydrocephalus and increased intracranial pressure can also occur in the more advanced stages of the disease (Lin & Prados, 2016).

Brainstem gliomas can be focal or diffuse, each of the two types requires different treatment. Focal gliomas are typically located in the midbrain or medulla. They are characterised by slow progression, and can be managed effectively with surgery or even observation. However, the majority of brainstem gliomas are diffuse and arise in the pons, such as the Diffuse Intrinsic Pontine Glioma (DIPG). These are aggressive malignant neoplasms, for which radiotherapy and chemotherapy are currently the standard treatment (Lin & Prados, 2016).

**1.2 Long-term complications subsequent to PFT diagnosis and treatment**

**1.2.1 Motor deficits**

Coordination and motor deficits are reported in up to 50% of all childhood brain tumour survivors (Packer et al., 2003), but this figure may be even higher for PFT patients, considering the pivotal role of the cerebellum in the modulation of movement. Numerous studies have reported deficiencies in fine and gross motor skills in long-term paediatric PFT survivors. Reported impairments include poor coordination, balance and fine motor control (Callu et al., 2009; Ruekriegel,
Blankenburg, Henze, & Baque, 2009; Davis, Pitchford, Jaspan, McArthur, & Walker, 2010; Davis, Pitchford, Jaspan, McArthur, & Walker, 2013; Küper et al., 2013), reduced physical activity and agility (Odame et al., 2006; Piscione, Bouffet, Mabbott, Shams, & Kulkarni, 2013), and disrupted sensory-motor synchronisation (Provasi et al., 2014). Malignant tumours have been reported to result in more profound motor deficits, compared to benign tumours (Callu et al., 2009; Rueckriegel, Blankenburg, Henze, Baqué, & Driever, 2009).

1.2.2 Cognitive deficits

Cognitive deficits following PFT in childhood in regard to IQ, memory, attention and executive function have been examined by numerous studies (e.g., Dennis, Spiegler, Hetherington, & Greenberg, 1996; Holmquist & Scott, 2002; Aarsen et al., 2009; De Smet et al., 2009; Davis, Pitchford, Jaspan, McArthur, & Walker, 2011; Quintero-Gallego, Gomez, Morales, & Marquez, 2011; Davis et al., 2013; Droit-Vollet et al., 2013; Moberget et al., 2015) and summarised in narrative reviews (e.g., Cantelmi, Schweizer & Cusimano, 2008; Palmer & Leigh, 2009; Hanzlik, Woodrome, Abdel-Baki, Geller, & Elbabaa, 2015). A recent meta-analysis of the cognitive deficits in PFT survivors (Robinson et al., 2013) concluded that deficits are evident in overall cognitive ability, and verbal and non-verbal intelligence, with the effect sizes ranging from moderate (-.62) to large (-1.69). Similarly to motor deficits, cognitive impairments are more frequently reported in malignant tumour patients who receive radiotherapy as part of their treatment (Copeland, deMoor, Moore, & Ater, 1999); Rueckriegel et al., 2009, Piscione et al., 2014).
1.2.3 Quality of life and other functional deficits

Quality of life (QOL) is now considered an important indicator when evaluating the success of PFT treatment, largely due to the increasing survival rates and the fact that more paediatric PFT patients are entering adulthood. Studies in this area report varying outcomes. Overall, the QOL of the majority of PFT survivors is reported to be similar to the general population. A small proportion of patients report reduced quality of life, which has been associated with the lower socio-economic status of the family and permanent post-operative hydrocephalus treatment (Kulkarni, Piscione, Shams, & Bouffet, 2013). However, Pate, Mullins, O’Neil, & Wilson (2011) compared patients with infra-tentorial (PFT) and supra-tentorial tumours in a total sample of 70 and found that patients with infratentorial tumours generally reported lower QOL, demonstrating that PFTs are associated with an elevated risk of poor QOL, compared to other CNS tumours. Among other reported deficits are reduced abilities in terms of temporal discrimination, in particular short-duration perception (Hetherington, Dennis, & Spiegler., 2000; Droit-Vollet et al., 2013), an elevated risk of seizures, hearing and sight impairments (Packer et al., 2003), disruption of respiration during sleep (Lee, Chen, Abeshaus, Poliakov, & Ojemann, 2013), as well as reduced energy levels and overall physical functioning (Reimers, Mortensen, & Schmiegelow, 2009).

1.2.4 Language impairments

In addition to the aforementioned complications, a number of researchers have investigated possible long-term speech and language processing deficits in PFT survivors, beyond simple articulation and skills reliant on general cognitive abilities.
(e.g. verbal memory, which has frequently been investigated in studies of cognitive deficits, is largely underpinned by short-term memory abilities, rather than linguistic skills). Studies addressing this issue, published in the last 30 years, report a mixture of outcomes, from the preservation of speech and language abilities to severe impairments (e.g., Hudson & Murdoch, 1992; Huber, Bradley, Spiegler, & Dennis, 2007; Richter et al., 2005; Morgan et al., 2011). A systematic review of the studies, reporting on speech and/or language outcomes in long-term PFT survivors, is presented in Chapter 2. It will be demonstrated that the current evidence is sparse and inconclusive, and based on methodologically limited approaches, namely neuropsychological investigations and observations, without supporting evidence from neuroimaging. This is despite the fact that magnetic resonance imaging has been used to study the neural bases of language processing for over 25 years in both the healthy population and people with other medical conditions. Combining detailed neuropsychological profiling of speech and/or language difficulties in paediatric patients following treatment for PFT with structural and functional neuroimaging is needed to advance understanding in this area. This unique method of investigation forms that basis of the research conducted in this thesis.

1.3 Magnetic resonance imaging and its use in language research

1.3.2 Basic principles of the MRI

Magnetic resonance imaging (MRI) is a non-invasive method of visualisation of the internal organs and tissues that is widely used in modern clinical practice and research. Its origins stem from the discovery of nuclear magnetic
resonance (NMR) by physicists in 1946 (Huettel, Song, & McCarthy, 2004).

The MRI technique utilises the magnetic properties of hydrogen atoms, which are abundant in water and other molecules in the body. A positively charged hydrogen nucleus (proton) spins continuously about its own axis, thus generating a small magnetic field (magnetic moment). The application of a strong external magnetic field $B_0$ leads to the alignment of the protons along the direction of this field. All magnetic moments, aligned along the z-direction (parallel to the direction of the $B_0$ field), continue to precess about the direction of $B_0$ with the same frequency (Larmor frequency). A large number of protons, precessing at a constant frequency, can be represented by a group of vectors. The vector sum of all of the magnetic moments $M_0$ is a measurable quantity (Figure 1.6).

![Figure 1.6. Sum of the spin vectors producing net magnetisation. From (McRobbie, Moore, Graves, & Prince, 2017).](image)

In order to measure the magnetic moment $M_0$, a radiofrequency (RF) pulse is applied, which induces a fixed magnetic field $B_1$. It ‘flips’ the spins by 90° into the transverse
plane xy, also bringing them into phase. Once the RF pulse is switched off, the spin relaxation and dephasing process begins, until they align again in the z-direction, parallel to $B_0$. (Figure 1.7). The strength of the RF pulse can be changed, producing different flip angles; for example, an $180^\circ$ pulse will turn the spins the opposite way to their initial direction.

![Figure 1.7. Schematic illustration of the net magnetic moment being ‘flipped’ into the xy plane by an RF pulse, generating a static magnetic field $B_1$. From (McRobbie et al., 2017).](image)

Rotated $M_0$ induces a voltage, which is detected by the receiver coil. As the spins relax, the detected signal decays over time. The relaxation of the spins is determined by other nearby spins with which they interact, and by the properties of the tissue. The spin-spin relaxation, or dephasing in relation to other spins, is characterised by the time $T_2$. The spin-lattice relaxation, or recovery of the equilibrium state in the $B_0$ field, is characterised by the time $T_1$. $T_1$ recovery is much slower than $T_2$ relaxation (or decay); several seconds to a few hundred milliseconds respectively (Huettel et al., 2004). The differences in the $T_1$ and $T_2$ times in different tissues are utilised to generate $T_1$-weighted and $T_2$-weighted contrast images, which are widely used in clinical practice and research (Figure 1.8; Table 1.1). The T2*-weighted contrast also takes
into account inhomogeneities of the magnetic field, in addition to the spin-spin interaction. Thus the $T_2^*$ contrast is sensitive to the amount of deoxygenated haemoglobin in the tissue, and this property is utilised in the blood-oxygenated level dependent (BOLD) contrast used in functional MRI, the methodology of which is detailed in Chapter 4. Due to the added effects of the spin-spin interactions, and the magnetic field inhomogeneities, the $T_2^*$ relaxation time is shorter than $T_2$.

![Illustration of the temporal relationship between $T_1$ relaxation and $T_2$ decay](image)

*Figure 1.8. Illustration of the temporal relationship between $T_1$ relaxation and $T_2$ decay. From (McRobbie et al., 2017).*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$T_1$ (ms)</th>
<th>$T_2$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter</td>
<td>832</td>
<td>110</td>
</tr>
<tr>
<td>Grey matter</td>
<td>1331</td>
<td>80</td>
</tr>
</tbody>
</table>

By combining RF pulses and gradients in different ways, a large number of scan sequences have been developed since the first conception of the MRI technique, each resulting in a different appearance of the tissue of interest (contrasts). Different contrasts are used to examine the structural and
functional properties of the grey and white matter. For example, T1-weighted sequences are used to investigate the anatomical structure and volume of the neural tissue; T2*-sequences are used for examining metabolic activity; and T2-sequences with added diffusion gradients are used to study the water distribution in the neural tissues.

**1.3.3 MRI in language research**

MRI has proven to be an invaluable tool in research concerned with the neural correlates of language processing. Since the early 1990s, MRI has been increasingly utilised in language studies, to supplement a large body of behavioural and lesion-related evidence.

**1.3.3.1 Structural imaging**

Broadly, language-related MRI investigations can be segregated into structural and functional studies. Structural studies investigate experience-dependent changes in the GM and WM within the structures thought to support language function (Richardson & Price, 2009). The most commonly used approaches are voxel-based morphometry (VBM) and diffusion tensor imaging (DTI). VBM (Ashburner & Friston, 2000) involves voxel-by-voxel analysis of high-resolution structural T1-weighted MRI images. After tissue segmentation, both white and grey matter can be compared between groups of subjects, or before and after a behavioural intervention, such as a learning experience. VBM can be used for a variety of purposes, for example, to investigate the relative density of the GM/WM in relation to other tissues in the region, or the volume differences of the GM/WM in different regions (Mechelli, Price, Friston, & Ashburner, 2005). The VBM method has been applied in a number of language studies, such as
the processing of speech, bilingualism-related structural plasticity and dyslexia, among others (e.g., Golestani, Paus, & Zatorre, 2002; Mechelli et al., 2004; Richlan, Kronbichler, & Wimmer, 2013).

The DTI technique has been used to study the structural viability of the white matter tracts implicated in language processing. The method, which is described in more detail in Chapter 5 of this thesis, is built on the assumption that the diffusion of hydrogen protons, which are abundant in the extracellular space, is more anisotropic within structurally sound, healthy WM tracts than in damaged WM tracts.

Conversely, microstructural deterioration of the WM will result in a more random (isotropic) distribution of water in the tissue than in healthy WM tracts (Beaulieu, 2002). Tractography is one specific application of DTI that enables the tracing of the MW connections between selected regions. Much of the language-related DTI work has been focused on studying the WM connections of the perisylvian language regions, more specifically, the arcuate fasciculus (AF). In a seminal study, Catani, Jones, & ffytche (2005) described the precise anatomy of the AF, as consisting of a direct long segment of fibers connecting Broca’s and Wernike’s territory, and an indirect connection between the two via Geschwind’s territory, consisting of two short anterior and posterior segments.

Further studies have confirmed the involvement of other WM pathways in the modulation of the semantics of language, including the uncinate fasciculus, the inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus (Catani & Mesulam, 2008a). In addition, commissural fibers have been implicated in the linguistic functions where inter-hemispheric connections may be required (Smits, Jiskoot, & Papma,
2014). For example, some DTI studies on developmental dyslexia have suggested the involvement of the posterior corpus callosum in this disorder (Vandermosten, Boets, Wouters, & Ghesquière, 2012).

1.3.3.2 Functional imaging

In contrast to structural techniques, functional MRI (fMRI) has proven to be much more popular for studying neural correlates of language, as it affords a dynamic exploration of language processing in real time, largely due to its non-invasive nature and the absence of radioactive exposure, which was an issue with its predecessor, Positron Emission Tomography (PET). A typical fMRI study of language would involve a linguistic task, designed by the researcher and performed by the participant inside the scanner. In the 25 years of fMRI language research, a whole body of literature has emerged on the methodology of designing the best fMRI paradigms to explore different language functions (Amaro & Barker, 2006; Bookheimer, 2009); this is discussed in more detail in Chapter 4 of the present thesis.

The increase in the popularity of the method has happened despite the multiple methodological challenges associated with imaging language processing. For example, the execution of speech movements produces significant motion artefacts that can distort the localisation of the activation. Another problem is that the change in signal measurable by the fMRI is very small (3-5%) and due to the sluggish nature of the BOLD response it can only be detected 6-7 seconds after the stimulus onset (Dogil et al., 2009). Finally, fMRI demonstrates poor sensitivity in single-subject studies; thus, the reliability of the results is directly dependent on the study sample size.
Despite the practical challenges, fMRI has become a primary tool for in-vivo investigation of the neural basis of language processing, and has greatly enriched the modern understanding of the neuroanatomy of language. Price (2012) carried out a comprehensive review of the first 20 years of the application of fMRI to study several aspects of language processing in the healthy population, namely speech production, speech comprehension, and reading. The author presented a theoretical model of the relationship between the linguistic functions and their anatomical associations, extending the previous PET-based model of Petersen et al. (1998, 1999). As well as confirming the role of the perisylvian regions in language processing, the review highlighted other cortical and subcortical regions that are activated during language processing, including the superior frontal gyrus, the supplementary motor cortex, cerebellar lobules VI and VII, the caudate nucleus, the globus pallidus and the thalamus. Given involvement of the cerebellar lobules VI and VII in language processing in the healthy population, it is timely to investigate the impact of cerebellar involvement in language processing in patients that have undergone treatment for PFT during childhood.

1.4 Present investigation

1.4.1 Objective

The primary aim of this thesis is to reveal previously unexplored neural correlates of language processing in PFT survivors, specifically, task-related cortical activation patterns and changes in the microstructural integrity of the WM.
Functional and structural MRI methods will be applied in addition to the detailed, systematic neuropsychological assessment, as these methods have previously been effective in the study of language processing in healthy population and patients with other medical conditions.

1.4.2 Ethical considerations and funding

The study protocol was designed by the author and approved by the academic supervisors (Appendix 1). Ethical approval for the study was obtained from the East Midlands NHS Research Ethics Committee (see the letter of approval in Appendix 2). In addition, Nottingham University Hospitals (NUH) Research and Innovation department reviewed the project and granted access to the NUH patient database (Appendix 3). The University of Nottingham acted as a study sponsor. A formal letter of support for the study was also received from the NUH Paediatric Oncology department.

Funding for the project was jointly provided by the Children's Brain Tumour Research Centre and the School of Psychology, University of Nottingham. Twenty-five hours of scanning were funded by the Sir Peter Mansfield MRI centre. An additional grant towards the scanning costs was received from the Nottingham Hospitals charity.

1.4.3 Methodology

Within the available time-scale, an analytical observational methodology was considered to be the most feasible approach. Analytical studies allow the testing of hypotheses in order to make inferences about the relationships between the exposures and outcomes (Song & Chung, 2010). Within this framework, a retrospective cohort design was chosen as the most suitable, as it enabled the precise definition of the
studied clinical group (patients who sustained PFTs before the age of 16) and outcomes of interest (overt language performance, associated cortical metabolic response and measures of the WM microstructural integrity).

Retrospective cohort studies are particularly suitable for studying rare exposures and common outcomes. Indeed, PFT occurrence is a lot less common than language disorders. While around 300 cases of paediatric posterior fossa tumours are recorded each year in the UK (The Brain Tumour Charity, 2016a), the estimated prevalence of additional speech, language and communication impairments in children and young people in England alone is around 21% among children of school age (Department for Education, 2016).

The present study employed a multi-modal methodological approach, combining neuropsychological assessment, task-based fMRI, DTI, and clinical profile analysis. In addition, a systematic review of the literature was performed prior to conducting the study, in order to clarify what is currently known about the language abilities of PFT survivors in the long-term recovery phase. Chapters 2, 3, 4, 5 and 6 report the findings from each strand of the present project, and Chapter 7 contains a general discussion. Table 1.2 provides the details for each strand and its main aim.

**1.4.4 Summary**

Paediatric posterior fossa tumour survivors display a range of long-term functional deficits, including motor, cognitive, affective and neurological impairments. Speech and language abilities are also likely to be affected, considering the anatomical connectivity between the cerebellum and cerebrum, and growing awareness of the cerebellar role in
Table 1.2.
*Summary of the project components, reported in the chapters of the present thesis*

<table>
<thead>
<tr>
<th>Project component</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review of the literature</td>
<td>To summarise and critique current evidence of long-term speech and language deficits in PFT population and to identify what needs to be done to move the field forward</td>
</tr>
<tr>
<td>Neuropsychological investigation</td>
<td>To systematically evaluate the language, cognitive and manual dexterity skills in a cohort of long-term PFT survivors, using neuropsychological assessment, and compare these to the matched healthy control group in order to detect any developmental deviations from the norm. For the first time, the relative contribution of each linguistic and non-linguistic function to the between-group differences will be analysed, using discriminant function analysis.</td>
</tr>
<tr>
<td>Functional MRI study</td>
<td>To examine, for the first time, cortical activation patterns associated with performance of PFT patients and healthy age-matched controls during tasks of covert articulation and semantic retrieval</td>
</tr>
<tr>
<td>DTI study</td>
<td>To examine, for the first time, microstructural integrity of white matter and associations with level of language performance in PFT patients compared to healthy age-matched controls.</td>
</tr>
<tr>
<td>Clinical profiles study</td>
<td>To evaluate the relationship between the patients’ clinical histories and speech and language outcomes by applying cluster analysis technique, previously not used in this population group. In addition, for the first time, the relationship between oro-motor functioning and presence of the underlying language disorder in PFT survivors will be explored.</td>
</tr>
</tbody>
</table>
language modulation. So far, studies of the communication
deficits in this patient population have relied exclusively on
behavioural evidence and produced a range of mixed findings.
Magnetic resonance imaging provides a means to study the
neural correlates of language processing non-invasively, yet it
has not been used for this purpose in the PFT population so
far. A study is proposed that will combine a detailed
neuropsychological assessment of speech and language
abilities with functional and structural MRI in order to
investigate if PFT survivors display communication deficits in
the long-term recovery phase, and if there are associated
changes in their brain structure and functioning.
Chapter 2: Long-term speech and language outcomes in survivors of childhood posterior fossa tumours: a systematic qualitative review of the literature

Key findings

- The published literature on long-term speech and/or language outcomes in paediatric PFT survivors is evaluated;
- There is a long-standing awareness of the potential adverse impact of PFTs on speech and language;
- The findings are mixed and sometimes contradictory;
- Most frequently, impaired speech and/or language abilities are associated with radiotherapy, medulloblastoma and post-operative mutism;
- About half of the studies compare patients’ performance to normative data rather than control groups, which undermines their ecological validity;
- More systematic, structured observational research is needed in order to clarify which specific aspects of communication disorders are present in PFT survivors.

2.1 Introduction

Language, as a way of exchanging messages via the production, perception and comprehension of speech, is a unique characteristic of the human species. This is due to the complexity of the highly developed nervous system and speech production apparatus. Because both aspects are necessary for effective communication, associated disorders are often referred to by the umbrella term ‘speech and language disorders’. Broadly, three major classes of such disorders have been identified: aphasia, dysarthria and apraxia.
Aphasia is a group of language disorders, characterised by an impairment in the organisation and symbolic formulation of concepts. Both apraxia and dysarthria are disorders of the regulation of language production, yet, aetiologies of these conditions are distinctly different. In apraxia, the impairment is associated with poor planning and programming movement gestures of speech due to the damage to the cerebral cortex. Commonly this occurs as a result of stroke or neurodegenerative conditions impacting language-associated cortical regions, such as Broca’s area (Strand, Duffy, Clark, & Josephs, 2014). Dysarthria is a neuromuscular disorder that can arise as a result of damage to either central or peripheral nervous system, leading to the disruption of neural signal transmission necessary for controlling the motor regulation of speech. Ataxic dysarthria, first described as “scanning speech” in 1877 is a sub-type that occurs as a result of the damage to the cerebellum or its input and output pathways (Spencer & Slocomb, 2007).

Proficiency in speech and language are key for maintaining social engagement and scholastic progression (Tomblin, Zhang, Buckwalter, & Catts, 2000; Petersen et al., 2013). At the same time, research has shown that childhood brain tumour survivors are likely to experience communication difficulties and social isolation, leading to a poorer quality of life overall (Bhat et al., 2005). While this is to be expected in the case of supratentorial tumours, in particular those affecting the areas of the canonical perisylvian language network (Catani & Jones, 2005), in the case of infratentorial tumours, the association between the disease and a
subsequent language disorder is much less obvious. Since the early 1990s, the involvement of the cerebellum in speech and language modulation has been debated by neuropsychologists and linguists (Parvizi, 2009; Fiez, 2016). This development has largely been informed by the growing use of functional MRI in linguistic research, which has demonstrated cerebellar activation during speech articulation and language processing tasks in healthy populations (e.g., Ackermann, Wildgruber, Daum, & Grodd, 1998; Xiang, Lin, Ma, Zhang, & Bower, 2003; Booth, Wood, Lu, Houk, & Bitan, 2007). The evidence that has emerged as a result of these studies suggests that the cerebellum is involved in the modulation of language-related functions, including speech and language perception, speech motor planning, verbal working memory, verbal fluency, grammatical processing, and the dynamics of language production and writing (Marian et al., 2014; Stoodley, & Schmahmann, 2015).

Consistent with the growing awareness of the cerebellar role in language processing, a number of neuropsychological investigations in the past three decades have pointed out that infratentorial tumours may increase the risk of speech and language complications, ranging from acute complications immediately post-treatment, to chronic deficiencies extending into the long-term recovery phase. Arguably, the most discussed acute speech impairment is Cerebellar Mutism Syndrome (CMS), which manifests as a total absence of verbal response following surgical tumour resection, and is reported in up to 30% of patients (Palmer et al., 2010; Law et al., 2012). The effect is transient and patients eventually
regain functional speech. At the same time, the long-term consequences for speech and language function in PFT survivors, with or without CMS, have received much less attention in the literature.

The present systematic review was conducted with a view to summarising the existing literature addressing the question of long-term speech and language functioning in paediatric PFT survivors. The following aims were pursued:

- To identify all published English-language studies addressing the topic of interest;
- To assess the methodological scope and quality of the reviewed studies;
- To evaluate the level of agreement between the findings reported in the studies;
- To identify the key risk factors, highlighted in the reviewed studies, that may be implicated in adverse speech and/or language outcomes;
- To discuss persistent themes emerging from the reviewed studies.

2.2 Method

2.2.1 Search strategy

The main literature search was performed in December 2015. To produce an updated literature search, an automated search was performed monthly since December 2015 until June 2017 with no new relevant publications added to the results of the December 2015 search. The OVID databases Medline, PsychInfo and Embase were searched for eligible studies using the following strategy. First, the databases were searched for the term "brain tumour" or "brain tumor" using the Medical Terms Subject Heading (MeSH) option and relevant sub-headings. Next, the databases were searched for the following keywords: 'cerebellum' OR
‘posterior fossa’ OR ‘fourth ventricle’ OR ‘brainstem’, in order to identify studies focusing on posterior fossa tumours. Then the two searches were combined and limited to peer-reviewed publications in English, with humans aged 0-18 years. Finally, the obtained sample of studies were searched using the following terms: ‘l?ngu*’ OR ‘speech’ OR ‘dysarthria’ OR ‘mutism’ OR ‘tongue move*’ OR ‘vocali?at*’ OR ‘verbal’. In addition, the reference lists of the retrieved articles were searched for eligible studies.

2.2.2 Inclusion criteria

The selection criteria for the reviewed articles were as follows: i) All patients in the study were diagnosed with PFT before their 16\textsuperscript{th} birthday, ii) Assessments of patients’ speech and/or language abilities were carried out at least 12 months post-diagnosis; iii) At least one domain of speech or language functioning was assessed in the study (such as language production, comprehension, semantic processing, articulation, reading, writing etc.); iv) Group-level analysis was performed, comparing PFT patients to a healthy control group or a normative sample.

Case reports and small case series without a comparison to healthy controls or normative samples were not included as they would not be helpful in establishing whether communication skills are impaired or preserved. Studies where group analyses were reported but not all patients satisfied the inclusion criteria were also excluded. Studies reporting only verbal IQ index and/or verbal memory index were not included as these indices are commonly regarded as measures of general cognitive rather than linguistic ability.
Chapter 2

Data extracted from all publications included the patient sample size, gender, time since diagnosis, speech and language domains assessed, and measures used. Where available, information was also extracted about the size of the control group, tumour histology, tumour location and the presence of adjuvant therapy. Studies were evaluated for quality by the author, using a Critical Appraisal Skills Programme (CASP UK, 2016) cohort studies evaluation tool. Although not all of the reviewed studies strictly followed the cohort design, this tool was considered to be the most appropriate among those available as part of the CASP framework.

2.3 Results

Figure 2.1 illustrates the retrieval process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). Table 2.1. summarises the quality assessment for the studies, according to the CASP framework.

Nine articles met the inclusion criteria and were included in the final review. The studies were conducted in several countries, including Australia, the Netherlands, Germany, the USA, Canada, Spain and the UK, and collectively report on language outcomes in at least 182 long-term survivors of childhood PFTs. The precise numbers of patients are difficult to determine, as the patient samples in Aarsen et al. (2004) and Aarsen et al. (2009) partly overlap. After contacting the author, it was not possible to establish the degree of this overlap. As these two studies report different outcome measures, both are included.

The largest reported sample in a single study is 54 patients (Huber et al., 2007). Speech and/or language was the
primary focus of investigation in four studies (Hudson and Murdoch, 1992; Huber, Bradley, Spiegler, & Dennis, 2007; Richter et al., 2005; Morgan et al., 2011). Other studies considered language in the context of wider cognitive functioning (Copeland, Moore, & Ater, 1999; Aarsen et al., 2004; Vaquero, Gómez, Quintero, González-Rosa, & Márquez, 2008; Aarsen et al., 2009; Edelstein et al., 2011). The studies differ vastly in terms of their methodological approach (e.g. sample size, inclusion criteria, follow-up period, choice of control groups, assessment tools, and consideration of relevant clinical history). These issues, their impact on the quality of the studies and the overall findings are discussed.

Table 2.2 provides a concise summary of the group-level outcomes in speech and/or language functioning from the reviewed studies. The findings are separated into speech abilities and language abilities, as these categories are frequently used to delineate different aspects of communication disorders. All difficulties related to speech production have been considered, such as articulation, prosody, fluency of speech, voice quality etc. In contrast to speech pathology, language disorders manifest as lower than age-appropriate language skills despite normal sensory abilities and environmental exposure. Core and higher-order language abilities are reported separately, as core language skills typically encompass expressive and receptive language abilities, phonological awareness, language structure and content, while higher-order language skills usually refer to the understanding of multiple meanings and idioms, the ability to make inferences and understanding ambiguous sentences (e.g. Docking, Murdoch, and Suppiah, 2007).
Table 2.3 presents the details of each study with the description of the specific measures used and the reported findings. Table 2.4 provides a summary of the risk factors found to be associated or not associated with the adverse long-term speech and/or language outcomes. Finally, Table 2.5 contains the details of highly relevant studies that did not fully satisfy the inclusion criteria for the systematic review. Information about these studies has been included in order to construct a more comprehensive picture of the current state of knowledge around the research question.
Figure 2.1. Article identification algorithm according to PRISMA guidelines
Table 2.1
CASP checklist for quality evaluation of the articles included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
<th>Q11</th>
<th>Q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudson and Murdoch (1992)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell*</td>
<td>N/A</td>
<td>Mild language impairments</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Evidence of the adverse side-effects of the disease</td>
</tr>
<tr>
<td>Copeland et al. (1999)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Language impairments in RT-treated patients</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Evidence of the adverse side-effects of the RT treatment</td>
</tr>
<tr>
<td>Aarsen et al. (2004)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td>Varying degree of language deficits</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Evidence of the deficits in non-RT treated patients</td>
</tr>
<tr>
<td>Aarsen et al. (2009)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Deficits in naming. Brainstem tumour patients – additional deficits in verbal intelligence and memory</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Evidence of the specific deficits and effects of tumour location</td>
</tr>
<tr>
<td>Vaquero et al. (2008)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Severe deficits in MB patients, moderate deficits in AC patients</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Need for devising separate rehabilitation strategies for different clinical groups</td>
<td></td>
</tr>
<tr>
<td>Edelstein et al. (2011)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Signs of early ageing in PFT survivors, including language deficits</td>
<td>Wide CIs</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Evidence of the chronic deficits in a growing population of the long-term PFT survivors</td>
</tr>
</tbody>
</table>
Table 2.1 (Continued)
*CASP checklist for quality evaluation of the articles included in the systematic review*

<table>
<thead>
<tr>
<th>Study</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
<th>Q11</th>
<th>Q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter et al. (2005)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>No language deficits in AC patients</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Absence of the adjuvant treatment may serve as a protective factor</td>
<td></td>
</tr>
<tr>
<td>Morgan et al. (2011)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Dysarthria irrespective of the post-operative mutism</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Evidence of the dysarthria irrespective of the tumour type</td>
<td></td>
</tr>
<tr>
<td>Huber et al. (2007)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Speech disfluency evident in all patients, ataxic dysarthria in MB patients</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Evidence of reduced speech fluency irrespective of the tumour type</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Q1. Did the study address a clearly focused issue? Q2. Was the cohort recruited in an acceptable way? Q3. Was the exposure accurately measured to minimise bias? Q4. Was the outcome accurately measured to minimise bias? Q5. Have the authors identified all important confounding factors? Q6. Was the follow-up of subjects complete enough? Q7. What are the results of the study? Q8. How precise are the results? Q9. Do you believe the results? Q10. Can the results be applied to the local population? Q11. Do the results of this study fit with other available evidence? Q12. What are the implications of the study for practice?

MB – Medulloblastoma, AC – Astrocytoma, RT – Radiotherapy

*Definitive answer could not be given due to the lack of the information in the article
N/A – question is not relevant to the study design*
### Table 2.2

**Summary of the reported speech and/or language outcomes preserved (P), impaired (I) or at the borderline level (BL) in long-term PFT survivors. Summary reflects the group and sub-group level analyses**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>T</th>
<th>Speech and dysarthria</th>
<th>Core language skills</th>
<th>Advanced language skills</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LD</td>
<td>CN</td>
</tr>
<tr>
<td>Hudson and Murdoch (1992)</td>
<td>20</td>
<td>&gt;14</td>
<td>I/P</td>
<td>I/P</td>
<td></td>
</tr>
<tr>
<td>Copeland et al. (1999)</td>
<td>21*</td>
<td>&gt;12</td>
<td>I/P</td>
<td>BL</td>
<td>BL</td>
</tr>
<tr>
<td>Aarsen et al. (2004)</td>
<td>23*</td>
<td>&gt;12</td>
<td>I/P</td>
<td>I/P</td>
<td>P</td>
</tr>
<tr>
<td>Aarsen et al. (2009)</td>
<td>35*</td>
<td>&gt;36</td>
<td>I</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Vaquero et al. (2008)</td>
<td>20*</td>
<td>&gt;5</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Edelstein et al. (2011)</td>
<td>20*</td>
<td>&gt;78</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richter et al. (2005)</td>
<td>11</td>
<td>&gt;12</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Morgan et al. (2011)</td>
<td>13</td>
<td>&gt;16</td>
<td>I/P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huber et al. (2007)</td>
<td>54</td>
<td>&gt;56</td>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.** *Performance was compared to normative sample and not compared to the control group.*

N = sample size, T = time post treatment (months), RT = received radiotherapy, NoRT = did not receive radiotherapy, MB = medulloblastoma, A = astrocytoma, LD = Language Development, CN = Confrontational Naming, RL = Receptive Language, EL = Expressive Language, SF = Semantic Fluency, PF = Phonologic Fluency
### Table 2.3
*Long-term speech and language outcomes in PFT survivors – detailed overview of the studies, reporting Preserved (P), impaired (I) or borderline (BL) functioning*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient sample size and description</th>
<th>Control group</th>
<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudson and Murdoch (1992)</td>
<td>PFT = 20, age-matched controls, normative sample</td>
<td>20 age-matched controls, normative sample</td>
<td>14 months to 7 months 3 years post-surgery</td>
<td>Test of Language Development Primary (TOLD-P) I, or Test of Language Development Intermediate (TOLD-I) I or Test of Adolescent Language -2 (TOAL-2) P Sub-tests of the Clinical Evaluation of Language Fundamentals (CELF -Producing Word Series, Producing Names on Confrontation, Producing Word Associations) P The Token Test I The Boston Naming Test P The Test of Language Competence (TLC) I</td>
</tr>
<tr>
<td>Copeland et al. (1999)</td>
<td>PFT = 21, diagnosed at &lt; 36 months of age</td>
<td>Normative sample, also RT vs NoRT</td>
<td>At least 12 months</td>
<td>Different tests at the individual follow-up appointments: Wechsler Subtests (Information, Similarities, Comprehension Peabody Picture Vocabulary Test, Word Fluency) PFT group overall BL compared to normative sample But RT I compared to NoRT</td>
</tr>
<tr>
<td>Study</td>
<td>Patient sample size and description</td>
<td>Control group</td>
<td>Time post-treatment</td>
<td>Assessment measures and reported outcomes</td>
</tr>
<tr>
<td>---------------</td>
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<td>--------------------------------------------</td>
</tr>
<tr>
<td>Aarsen et al. (2004)</td>
<td>AC = 23</td>
<td>Normative sample</td>
<td>Between 12 months and 8 years 10 months after resection</td>
<td>Test for Reception of Grammar (TROG), dysarthria assessment, verbal fluency test. 30% of the sample I language problems (word finding difficulties, non-fluent speech, semantic-pragmatic problems and phonological agraphia). 20% of the sample I speech problems/ dysarthria (disturbances of vocal quality articulation problems, slow speech rate, voice tremor)</td>
</tr>
<tr>
<td>Aarsen et al. (2009)</td>
<td>PFT = 35 BS=6 CB=29</td>
<td>Normative sample</td>
<td>Median =3 years, 6 months</td>
<td>Boston naming test (BNT) I  Verbal fluency P  Tokentest - language comprehension P</td>
</tr>
<tr>
<td>Vaquero et al. (2008)</td>
<td>MB =7 AC= 13 (10 female and 3 male)</td>
<td>HC = 12</td>
<td>AC: Mean = 3.25 (SD = 2.74) years from surgery MB: Mean = 6.47 (SD = 2.77) years from surgery</td>
<td>Controlled Oral Word Association Test (letter and animal categories), MB group (in particular V) semantic and phonological fluency I AC group: semantic fluency (animals) I</td>
</tr>
</tbody>
</table>
Table 2.3 (Continued)

Long-term speech and language outcomes in PFT survivors – detailed overview of the studies included in the systematic review, reporting preserved (P), impaired (I) or borderline (BL) functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient sample size and description</th>
<th>Control group</th>
<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edelstein et al. (2011)</strong></td>
<td>MB =20, 14 male Normative sample</td>
<td>Median time since diagnosis, 15.5 years (range, 6.5–42.2 years).</td>
<td>Controlled Oral Word Association (COWAT) test - Phonemic fluency I</td>
<td></td>
</tr>
<tr>
<td><strong>Richter et al. (2005)</strong></td>
<td>PFT = 12, 5 male All AC, No RT or ChT</td>
<td>HC = 27 1 year to 13 years 5 months</td>
<td>Naming task Verb generation task The Aachener Aphasietest (AAT) comprised of the Token Test and the Written language sub-test The Heidelberger Sprachentwicklungstest (German developmental language tests) Spontaneous speech analysis Speech analysis based on the syllable-repetition task and sentence-production task Group level: P</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.3 (Continued)

*Long-term speech and language outcomes in PFT survivors – detailed overview of the studies included in the systematic review, reporting preserved (P), impaired (I) or borderline (BL) functioning*

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<tr>
<th>Study</th>
<th>Patient sample size and description</th>
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<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
</table>
| Morgan et al. (2011) | MB = 6 A = 7 7 male                  | HC = 26       | 6 years 10 months (range 1;4 – 12;6 years) | Speech sample analysis (5 minute conversation and standard paragraph reading) I  
Verbal Motor Production Assessment for Children (VMPAC) P  
Motor Speech Profile I |
| Huber et al. (2007)    | MB = 25 A = 29 32 male              | HC = 40       | Mean time since surgery 13.42 years, range 4.83 – 31.42 years | Speech sample analysis  
The Dysarthria Rating Scale I |

Note: PFT – Posterior Fossa Tumour, MB – Medulloblastoma, AC – Astrocytoma, RT – radiotherapy, NoRT – no radiotherapy, ChT - chemotherapy
<table>
<thead>
<tr>
<th>Study</th>
<th>Tumour type</th>
<th>Tumour location</th>
<th>Post-operative mutism</th>
<th>Recovery time</th>
<th>Age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudson &amp; Murdoch (1992)</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Copeland et al. (1999)</td>
<td>Y</td>
<td></td>
<td></td>
<td>N</td>
<td></td>
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<tr>
<td>Aarsen et al. (2004)</td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
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<tr>
<td>Aarsen et al. (2009)</td>
<td></td>
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<td>Y</td>
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<tr>
<td>Vaquero et al. (2008)</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Edelstein et al. (2011)</td>
<td>Y</td>
<td></td>
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<td>Richter et al. (2005)</td>
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<tr>
<td>Morgan et al. (2011)</td>
<td>Y</td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Huber et al. (2007)</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

*Note. MB – medulloblastoma, AC - astrocytoma*
Table 2.5
Highly relevant studies that did not satisfy all of the inclusion criteria for the systematic review, reporting preserved (P), impaired (I) or borderline (BL) functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient sample size and description*</th>
<th>Control group</th>
<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
</table>
| Hudson et al. (1989) | PFT = 6                               | Normative sample | At least 12 months post-resection | The Fisher-Logemann Test of Articulation Competence, The Frenchay Dysarthria Assessment, Test of language development or Test of Adolescent language (age-dependent), CELF subtests (Producing word Series, Producing word associations, Producing names on confrontation) I or P subject-dependent
Mutism and radiotherapy predict poorer language outcomes
A connected speech sample (Picture shown and a question "What happens next?" asked) I or P subject-dependent |
| Steinlin et al. (2003)| PFT = 22, 7 female                    | Normative sample | 7.5 years post surgery (range 2.1 to 18.25 years) | Verbal fluency test (words beginning with F/S or FBL, or animal naming, depending on the age of participants) I |

*PFT = Post-Fontanelle-Taschen-Wert
Table 2.5 (Continued)
Highly relevant studies that did not satisfy all of the inclusion criteria for the systematic review, reporting preserved $P$, impaired $I$ or borderline (BL) functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient sample size and description*</th>
<th>Control group</th>
<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levisohn et al. (2000)</td>
<td>PFT = 2, both PA</td>
<td>Normative sample</td>
<td></td>
<td>Boston Naming Test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Verbal Fluency task</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I or P subject-dependent</td>
</tr>
<tr>
<td>Docking et al. (2005)</td>
<td>PFT = 5, 1 male</td>
<td>HC = 5, normative sample</td>
<td>1 year 6 months to 6 years 3 months post-treatment</td>
<td>Age-appropriate Test of Problem Solving, Test of Word Knowledge, Test of Language Competence – Expanded Edition, and either the Queensland University Inventory of Literacy (QUIL) or the Test of Phonological Awareness. As a group $P$ I in one case on higher language abilities and in one case on phonological awareness compared to normative sample</td>
</tr>
</tbody>
</table>
Table 2.5 (Continued)

Highly relevant studies that did not satisfy all of the inclusion criteria for the systematic review, reporting preserved P, impaired I or borderline (BL) functioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient sample size and description*</th>
<th>Control group</th>
<th>Time post-treatment</th>
<th>Assessment measures and reported outcomes</th>
</tr>
</thead>
</table>
| Docking et al. (2007)  | PFT = 2, both male                    | Normative sample | 1 year 2 months and 3 years post-treatment | CELF, 3rd ed, The Hundred Pictures Naming Test, The Peabody Picture Vocabulary Test –3rd ed P 
The Test of Word Knowledge, The Test of Language Competence, The Test of Problem Solving – Elementary, Revised P |
| Lewis and Murdoch (2010) | 3 fourth ventricle and/or cerebellum (all female) | HC 15, Each patient was matched with 5 controls | 2 to 5 years post-diagnosis | The Peabody Picture Vocabulary Test 3rd ed, The Hundred Pictures Naming Test; age-dependent CELF 4th ed or Preschool 2nd ed Group level: P 
Case analysis: 1 patient P, 2 patients I or P on different sub-tests 
Age-appropriate test from the Test of Problem Solving series and the Test of Language Competence—Expanded Edition Group level: P 
Case analysis: 1 patient P, 2 patients I or P on different sub-tests |

Note: *only patients at least 12-months post-treatment PFT – Posterior Fossa Tumour, MB – Medulloblastoma, AC – Astrocytoma, RT – radiotherapy, NoRT – no radiotherapy
2.4 Discussion

The literature review demonstrated a long-standing awareness of the language difficulties experienced by PFT survivors. The earliest identified studies date back to the late 1980s, although these are mostly case series, which may have limited their impact in the field. Several highly relevant studies did not fully satisfy the inclusion criteria for the systematic review, but are considered in a separate sub-section of the Discussion.

2.4.1 Observed deficits and their severity

The findings regarding the presence and severity of long-term speech and language impairments are mixed. Some studies report a deterioration in general and higher linguistic abilities in long-term PFT survivors (Hudson and Murdoch, 1992; Edelstein et al., 2011; Morgan et al., 2011), whereas other studies report variable outcomes ranging from normal to impaired functioning in various language domains resulting from specific tumour types or treatment regimes (Copeland et al., 1999; Huber et al., 2007; Vaquero et al., 2008; Aarsen et al., 2009). Moreover, two studies report no detectable abnormalities in patients’ speech and language, when analysed at a group level (Aarsen et al., 2004; Richter et al., 2005), although Aarsen et al. (2004) highlight the deficits in sub-groups of patients. The high variability in language outcomes may arise from wide discrepancies in the clinical histories of the patients reported. Acknowledging this, Murdoch and Hudson-Tennent (1994) argued that PFT patients should not be treated as a homogeneous group and that various risk factors must be taken into account when considering long-term outcomes.
2.4.2 Risk factors and predictors of poor language outcomes

It is evident from the reviewed studies that the risk factors for poor speech and language outcomes, discussed in the studies, bear a significant resemblance to the risk factors typically discussed in the context of cognitive impairments. These include radiotherapy, young age at diagnosis, hydrocephalus and perioperative factors (Riva & Giorgi, 2000; Reimers et al., 2003; Grill et al., 2004). This makes sense, since linguistic and cognitive abilities are highly interlinked and dependent on each other (Deak, 2004). Nevertheless, they are two separate domains, and there may be factors relevant to the development of speech and language that have not been duly appraised in the risk analysis of the reviewed studies, for example pre-tumour dyslexia, hearing difficulties or limited social interactions due to illness. Those risk factors that were highlighted in the reviewed studies are discussed.

2.4.2.1 Radiotherapy

Several studies suggest a link between radiotherapy and impaired language processing. For example, Copeland et al. (1999) observed that those patients who had received radiotherapy performed significantly worse on language tests compared to those who had not received radiotherapy. Furthermore, in the same study, developmental growth-curve analyses showed that the language performance in irradiated patients declined across time, while the performance of non-irradiated patients remained within developmental norms. Huber et al. (2007) reported that irradiated medulloblastoma patients displayed significantly more ataxic dysarthric features.
than non-irradiated survivors of astrocytomas and healthy controls. In contrast, the language performance of astrocytoma survivors who had not received radiotherapy did not differ significantly from that of the healthy controls. Likewise, Richter et al. (2005) reported no language impairments in non-irradiated patients, whilst Hudson and Murdoch (1992) could not clarify the effect of radiotherapy on speech and language functioning in a sample of 20 PFT patients, 14 of whom had received radiotherapy.

The absence of radiotherapy, however, does not guarantee intact language functioning. For example, Aarsen et al. (2004) assessed a group of 23 PFT patients treated without chemotherapy and radiotherapy, and reported that 30% of the patients experienced various language problems, including word finding difficulties, non-fluent speech, semantic-pragmatic problems and phonological agraphia. Thus, although the absence of radiotherapy may be a protective factor, significant language disturbance can occur even without the adjuvant therapy.

2.4.2.2 Tumour type

Although often considered an independent risk factor, tumour type is closely related to adjuvant therapy, as tumour histology directly influences the treatment regime. Medulloblastomas, the most aggressive type of tumour, typically require surgery, chemotherapy and radiotherapy, while less aggressive tumours, such as pilocytic astrocytomas, can be treated with surgery alone. Hence, poorer outcomes should be expected in childhood survivors of medulloblastoma compared to astrocytoma. In the study by Richter et al. (2005), all 11 patients with astrocytoma retained normal language functioning. In contrast, Edelstein et al. (2011)
reported significantly impaired phonological fluency in a sample of 20 adult survivors of childhood PFT with medulloblastoma, compared to a normative sample. Impairments in both phonological and semantic fluency have also been reported in medulloblastoma patients, particularly with vermal involvement, compared to astrocytoma patients and healthy controls (Vaquero et al., 2008). A number of speech deficits and the severity of dysarthria were also found to be worse for children with medulloblastoma, compared to children with astrocytoma (Morgan et al., 2011). In this study, however, all of the patients with medulloblastoma received adjuvant radiotherapy and chemotherapy, but none of the astrocytoma patients did, so effect of the tumour type was likely to be confounded by the treatment regime.

Notably, Aarsen et al. (2004), cautioned against the assumption that astrocytoma is a tumour type with a good long-term outlook for patients. In a group of 23 astrocytoma patients, whilst the majority (70%) retained normal language functioning, disturbed speech and language was observed in 30% of the patients. Similarly, Hudson & Murdoch (1992) reported that tumour type did not predict language performance in a sample of 20 PFT patients of mixed histology. Furthermore, Morgan et al. (2011) reported deviant speech features in all of their patients, and that tumour pathology did not predict severity of dysarthria.

Thus, whilst some studies have failed to establish the influence of tumour type on linguistic outcomes, other studies have suggested that poor language and communication outcomes are associated with medulloblastoma patients. Astrocytoma survivors typically display mild language deficits or intact language abilities, but the confounding influence of
treatment regime has not been fully quantified across studies. To differentiate tumour type from treatment regime, studies need to focus on one type of tumour that is treated in the same way across all patients. Other tumour types, besides medulloblastoma and astrocytoma, have not been sufficiently represented in the literature to draw firm conclusions.

2.4.2.3 Tumour location

The posterior fossa is comprised of several anatomical regions, including the cerebellum, the brain stem and the fourth ventricle. Tumours can develop at any of these sites, and links between tumour location and functional outcomes have previously been documented (Timmann & Daum, 2007; Koziol et al., 2014).

Several studies in the present review have reported on the link between tumour location and language outcomes. In the majority of cases these involve tumours in the cerebellum, which can be further segregated into the hemispheric (left or right), midline, or vermian location. Vaquero et al. (2008) found that cerebellar tumours involving the vermis were associated with poor performance on phonological and semantic fluency tasks. In addition, tumours impacting the dentate nucleus were associated with significantly poorer performance on semantic fluency tasks than tumours that do not affect this structure. Aarsen et al. (2009) also reported on the impact of tumours originating in the cerebellar hemispheres and brainstem. They presented a series of 35 patients, with 6 cases involving the brainstem and 29 cases involving cerebellar tumours. The results showed that left-sided cerebellar tumours were associated with an increased chance of experiencing receptive language difficulties. Brainstem tumours did not reliably predict language outcomes.
in a regression analyses. However, this subgroup of patients showed poor performance on the explicit naming task, suggesting that difficulties with expressive language may be associated with brainstem tumours. In addition, Morgan et al. (2011) found right cerebellar lesions to be associated more with poor speech production compared to left cerebellar lesions.

Thus, data regarding tumour location and subsequent language outcomes is sparse. The available evidence suggests that speech and language difficulties can originate from tumours arising in the brainstem or specific locations within the cerebellum. Currently, no studies have considered language outcomes in patients with tumours originating within the fourth ventricle, making it difficult to draw firm conclusions regarding the impact of tumour location on long-term language functioning.

### 2.4.2.4 Cerebellar mutism

Cerebellar mutism is a well-documented complication of posterior fossa tumour surgery, which manifests in the absence of any vocal response for days to weeks after surgical intervention (Tamburrini et al., 2015). It occurs in up to 30% of paediatric PFT patients and gradually resolves. Aguiar, Plese, Ciquini, & Marino (2005) and Pitsika & Tsitouras (2013) provide a detailed discussion of this complication and its acute impact on communication. There is, however, a debate over the impact of cerebellar mutism on long-term functional outcomes. Two studies reviewed here identified mutism as a risk factor for long-term speech and/or language impairments. Of the 20 patients reported by Hudson and Murdoch (1992), four experienced post-surgery mutism and all of them displayed long-term mild language processing
deficits. Likewise, two of the 23 patients reported by Aarsen et al. (2004) were mute post-surgery and both displayed speech and/or language difficulties at long-term follow-up. Systematic investigation of the effects of cerebellar mutism on language functioning is difficult due to the small number of cases, but it is necessary for the long-term prognosis and rehabilitation needs of this sub-group of patients to be fully understood.

2.4.2.5 Age at diagnosis and recovery time

Findings regarding the impact of age at diagnosis and time post surgery on late speech and language sequelae are contradictory. For example, within medulloblastoma survivors, a young age at diagnosis has been associated with weak literacy skills (Edelstein et al., 2011) and poor semantic fluency (Vaquero et al., 2008). In contrast, Copeland et al. (1999) reported that tumours diagnosed in infancy and treated without adjuvant therapy were associated with positive long-term outcomes in terms of language. Furthermore, Morgan et al. (2011) and Huber et al. (2007) found no clear association between either age at diagnosis or time post surgery and severity of long-term speech pathology, while Aarsen et al. (2009) reported that a longer interval between diagnosis and assessment negatively influenced language reception and verbal fluency. Thus, the relationship between the temporal factors and long-term speech and language outcomes is currently unclear.

2.4.2.6 Other risk factors

Pre-operative hydrocephalus is frequently cited as a contributor to post-tumour cognitive disturbances (Timmann & Daum, 2007). Hudson & Murdoch (1992) reported long-
term language difficulties in 70% of their sample, all of whom had experienced hydrocephalus prior to surgery. No other studies reviewed here explored this potential risk factor; thus there is a substantial need for further investigation of the role of pre-operative hydrocephalus in long-term speech and language outcomes.

Vaquero et al. (2008) investigated the risk associated with the extent of tumour resection and found that high-resected volume was predictive of good performance on phonological and semantic fluency tasks. This is consistent with the studies reporting inverse relationships between residual tumour volume and subsequent cognitive abilities (e.g. Aarsen et al., 2009).

### 2.4.3 Control group

Five studies compared patient performance to healthy matched volunteers (Hudson and Murdoch, 1992; Richter et al., 2005; Huber et al., 2007; Vaquero et al., 2008; Morgan et al., 2011). In other studies, normative sample data provided by psychometric test developers was used as a reference point. Although this is widely accepted practice, there are recognised limitations to standardised psychometric tests, as the majority have been developed with children from mainstream social strata, thus potentially disadvantaging those from low income, minority, or rural families. In addition, tests are typically standardised on local, not national, samples, making their national or international use problematic (Hedge & Pomaville, 2008). A study by Docking, Ward, & Murdoch (2005) illustrates the importance of comparing patient performance to matched healthy controls. They showed that the performance of patients did not differ statistically from the healthy controls on any of the language
measures administered. However, compared to standardised
norms, one patient demonstrated a reduced ability in higher
language skills, and another showed impaired phonological
awareness. Thus, the ecological validity of at least four of the
studies reported in this review is limited due to the lack of
matched controls (Copeland et al., 1999; Aarsen et al., 2004;
Aarsen et al., 2009; Edelstein et al., 2011). Future studies
should strive to use healthy volunteers matched to patients on
key demographics such as socio-economic status, age and
gender in order for appropriate comparisons to be made.

2.4.4 Highly relevant studies that did not fully
satisfy the review inclusion criteria

Several relevant studies were retrieved from the literature
search that did not satisfy all of the inclusion criteria but
nevertheless have contributed to the enquiry into the long-
term speech and language outcomes for PFT survivors.
Hudson, Murdoch, and Ozanne (1989) carried out an
investigation into post-PFT speech and language disturbances.
They described six such cases and noted that speech and
language disturbances are frequent but not inevitable
following treatment for PFTs in childhood. Mutism correlated
with long-term speech impairments; and radiotherapy
predicted poor language outcomes. No information on tumour
type or location was provided.

Docking et al. (2005) also described a case series of six
patients, all of whom had tumours to the brainstem.
Compared to standardised norms, one patient showed a
reduced ability in higher language skills, and another showed
impaired phonological awareness. These results contrast, to
some extent, with those of Aarsen et al. (2009) discussed in
the main review, who reported a clear deterioration of language in brain stem tumour patients. A later study by Docking et al. (2007) described a case series of four patients with cerebellar tumours, although only two patients were assessed over a year post-treatment. Both of these patients showed intact language abilities; both underwent total tumour resection, and neither was treated with radiotherapy. Hence, these cases may not be representative of the PFT patient population as a whole.

A further study by Steinlin et al. (2003) investigated neuropsychological long-term sequelae after PFT resection during childhood in a sample of 24 patients, 22 of whom were assessed at least 12 months post-treatment. They showed significantly impaired verbal fluency compared to the normative sample. However, this sample was very heterogeneous, both in terms of patient age and the length of time post-treatment. In addition, different word production tasks (phonological and semantic fluency tasks) were used for children of different ages that drew on qualitatively different cognitive processes (Costafreda et al., 2006).

A broad range of neuropsychological deficits have also been studied by Levisohn, Cronin-Golomb, and Schmahmann (2000), who reported a sample of 19 PFT survivors, of whom two were assessed at over a year post-treatment. Language function was impaired in one case and spared in the other.

Finally, Lewis and Murdoch (2010) presented a small case series of four posterior fossa tumour paediatric patients. Three of these patients were assessed over 12 months post diagnosis; all performed within or above the normal range on some tests and underperformed on others. In a follow-up
study, Lewis and Murdoch (2013) used developmental language trajectories to monitor the ongoing progress of these patients. These discussed above once again highlight the substantial inter-subject variability of language outcomes in PFT patients.

### 2.4.5 Conclusion

Significant discrepancies are apparent in the literature reporting long-term speech and language outcomes in childhood PFT survivors and this therefore warrants further investigations. To date, reports of both preserved and impaired speech and language functions in PFT survivors are common. The patients that most frequently suffer adverse outcomes in speech and/or language are those with a history of medulloblastoma, radiation treatment and post-operative mutism. The evidence is inconsistent or lacking regarding other risk factors, such as benign or rare tumour types, tumour location, age at diagnosis, time post surgery, extent of resection and pre-operative hydrocephalus. In addition, risk factors unique to the linguistic development domains such as dyslexia, sensory impairments or a lack of communication exposure are typically not considered at all. Approximately half of the studies use normative data as a reference point, which raises questions about their ecological validity.

There is a clear need for more structured observational research in order to document which specific speech and language domains are affected in PFT survivors, and which factors predispose patients to developing such deficits. Once more clarity has been achieved, it will be possible to devise intervention strategies to help affected patients to restore and preserve their communication abilities.
Chapter 3: Linguistic, cognitive and motor impairments in PFT survivors: a neuropsychological study

Key findings

- The method of integrated functional assessment is applied to demonstrate that PFT survivors underperform in language, non-verbal and manual dexterity, compared to healthy peers;
- In the most detailed language assessment to date in this group of patients, deficits are observed in the areas of language semantic content, expressive and receptive skills, verbal memory, reading and writing;
- Language skills, which are reliant on access to semantic content, contributed more to the between-group differences than non-verbal cognitive abilities;
- A significant association between language and non-verbal cognitive abilities in both patients and controls is unconfounded by the age and disease;
- Abnormally elevated heterogeneity of the patients’ linguistic profiles is quantified for the first time and is shown to be statistically significant;
- 24% of the patients demonstrate severe (below 2 SD) impairments on at least one assessment test.

3.1 Introduction

3.1.1 Neurodevelopmental bases of language processing

The systematic study of language development in childhood has its origins in the early twentieth century, in a classical publication ‘The Stern Diaries’, written by two pioneer developmental psychologists, who documented in great detail
language acquisition by their three young children (Shatz, 2009). In just over hundred years, the field has expanded enormously and remains popular with researchers around the globe. Much of the current interest is focused on the underlying neurodevelopmental mechanisms of language acquisition, largely due to the availability of advanced research methods, such as non-invasive neuroimaging techniques and computational simulations of the developing language networks. At the same time, behavioural neuropsychological assessment perhaps remains the most accessible, cheapest and reliable way of studying language development. The basic premise of neuropsychological evaluation is that normal or abnormal brain functioning can be inferred from behaviour, which, in turn, can be systematically recorded and evaluated (Lamberty & Greg, 2012). With the wide range of standardised neurocognitive tests available, language development can be assessed in children of all ages and health statuses.

Typically developing children become competent communicators by the age of five (Buckley, 2003). The rapid acquisition of linguistic skills is facilitated by the healthy development of the relevant neural systems, as well as sufficient external stimulation at the time when these systems are most receptive to such stimulation. The ‘sensitive period for language learning’ is a developmental neuropsychology concept, closely related to the concept of plasticity. Both describe the ability of the nervous system to adapt structurally and functionally in response to environmental demands and experiences (Newport, Bavelier, & Neville, 2001; Knudsen, 2004).
On the cellular level, language learning is thought to follow the principle of Hebbian learning: repeated stimulation of a neural circuit results in the strengthening and growth of its synaptic connections (Figure 3.1), which subsequently translates into more efficient overt language functioning (Hebb, 1949; Shafer & Garrido-Nag, 2009).

Figure 3.1. Branching out and strengthening of the neuronal connections in response to experience, based on the Hebbian learning principles. From (Knudsen, 2004)

It follows then, that language disturbances can be broadly attributed to either a lack of appropriate stimulation or faults in the supporting neural mechanisms, or indeed a mixture of the two. Language deficits resulting from damage to the neural tissue were first documented by the pioneers of clinico-neuropsychological assessment, Paul Broca (1824-1880) and Karl Wernicke (1848-1905). Broca established that damage to the inferior frontal gyrus results in speech production difficulties, while Wernicke described language comprehension deficits resulting from damage to the superior temporal gyrus (Figure 3.2). These observations laid the foundations for the modular understanding of language processing and the systematic neuropsychological assessment of language in clinical groups (Lamberty & Nelson, 2012).
3.1.2 Linguistic and other non-motor deficits subsequent to cerebellar damage

The impact of damage to the cerebral language-implicated regions (e.g., Broca’s and Wernicke’s areas) was studied extensively throughout the 20th century (Catani & Jones, 2005). At the same time, an appreciation of the involvement of the cerebellum in language processing developed at a much slower pace. One reason for this is the conventional understanding of the cerebellum as a structure responsible for the modulation of movement (for a review see Manto et al., 2012). In terms of behavioural assessment, damage to the cerebellum typically manifests itself in the loss of balance and poor coordination. These prominent signs often mask subtle non-motor deficits. In addition, many neuropsychological assessment tools often lack sensitivity in regard to detecting less obvious linguistic and cognitive impairments, arising as a result of damage to the cerebellum (Marien et al., 2013).
Despite the methodological challenges, over the recent decades a growing number of neuropsychological studies have investigated a broad range of non-motor deficits following cerebellar damage, including language processing difficulties (Leiner, Leiner, & Dow, 1993; Schmahmann, MacMore, & Vangel, 2009). In a seminal study, Schmahmann & Sherman (1998) proposed the concept of Cerebellar Cognitive Affective Syndrome (CCAS), based on the assessment of individuals with cerebellar damage of different aetiologies. The described non-motor impairments include language deficits such as agrammatism (a lack of functional words in the sentence structure) and dysprosodia (a lack of rhythm and appropriate intonation in speech). Other researchers, focusing predominantly on the posterior fossa tumour population, described Posterior Fossa Syndrome (PFS), a constellation of neurobehavioral deficits and affective deficits (Pollack, 1997; Catsman-Berrevoets & Aarsen, 2010) and the closely related Cerebellar Mutism Syndrome (CMS) or Mutism and Subsequent Dysarthria (MSD), which focuses more narrowly on post-operative temporary absence of speech (De Smet et al., 2007; Wells et al., 2008).

In recent years, there has been an initiative to reconcile the conflicting terminology used to describe overlapping cerebellum-related non-motor deficits. Figure 3.3 shows a currently widely accepted diagram of such symptoms and the conditions with which they have been associated (Gugrunardottir et al., 2016). Currently, Posterior Fossa Syndrome is considered to be the broadest, all-inclusive term. Different components and their combinations then contribute to CCAS, CMS and MSD.
From the neuroanatomical perspective, the involvement of the cerebellum in non-motor functions is thought to be facilitated by the dense reciprocal cerebello-cerebral white matter connections (Figure 3.4). These connections are discussed and investigated in more detail in Chapter 5 in the context of the diffusion tensor imaging (DTI) study of the white matter tracts subserving language processing. The specific ways in which the projections can be damaged during surgery and treatment are discussed in Chapter 6 in the context of the clinical predictors of adverse language outcomes.

Figure 3.3. Schematic diagram of the symptomatic spectrum of non-motor deficits subsequent to cerebellar damage described in the literature. Note. Entire outer circle - Posterior Fossa Syndrome; light grey area - Cerebellar Mutism Syndrome, dark grey area - Cerebellar Mutism; dotted area - Mutism and Subsequent Dysarthria; striped area - neurological cerebellar signs. From (Gudrunardottir et al., 2016).
3.1.3 Language-related functions of the cerebellum

Despite the mounting evidence from neuropathological studies, controversies still exist around the concept of the ‘linguistic’ cerebellum. In a recent consensus paper, the existing knowledge with regard to the involvement of the cerebellum in language processing was summarised (Marien et al., 2014). The most frequently reported language symptoms following cerebellar lesions include reduced verbal fluency and memory, impaired semantic access and agrammatic speech, and reading and writing impairments. Table 3.1 provides a summary of the evidence discussed in the consensus paper and studies published since then.
Table 3.1
Summary of the available evidence on the cerebellar involvement in different aspects of language, based on (Marien et al., 2014) and articles published between 2014 and 2017*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Proposed mechanism of cerebellar involvement</th>
<th>Supporting studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grammar processing</td>
<td>The cerebellum contributes to grammar processing in both the expressive and receptive domains. The majority of neuroimaging studies indicate that the right cerebellum is embedded within a distinct grammar processing network. Disruption of the cerebello-cerebral pathways results in impaired temporal coordination and recall of implicit internal representations of the grammatical rules of sentence structures.</td>
<td>Silveri et al. (1994); Ackermann et al. (1999); Gasparini et al. (1999); Justus (2004); De Smet et al. (2007); Marien et al. (2009); Fabbro et al. (2011); Leggio et al. (2011); Adamszek et al. (2012); Pliatsikas et al. (2014); Guell et al. (2015); Kepinska et al. (2017).</td>
</tr>
<tr>
<td>Speech and language perception</td>
<td>The cortico-cerebellar loops, among other cortical areas, target primary sensory and supramodal association areas. This indicates the involvement of the cerebellum in perceptual processes. Evidence from cerebellar patients and healthy volunteers suggests that the cerebellum is involved in the perception of certain temporal aspects of speech. Three related domains of speech perception, all related to the concept of timing, that seem to be supported by the cerebellum are i) distinct phonetic timing operations (e.g. pausing), ii) auditory signal segregation (e.g. pitch discrimination) and iii) cross-modal binding (e.g. simultaneous processing of visual and auditory information)</td>
<td>Ivry &amp; Gopal (1993); Ackermann et al. (1997); Ackermann et al. (1999); Mathiak et al. (2002); Mathiak et al. (2004); Petacchi et al. (2005); Ackermann (2008); Parsons et al. (2009); Sens et al. (2011); Stoodley &amp; Stein (2011); Powers et al. (2012); Schwartzte et al. (2012); Guediche et al. (2015).</td>
</tr>
</tbody>
</table>
Table 3.1 (Continued)
Summary of the available evidence on the cerebellar involvement in different aspects of language, based on (Marien et al., 2014) and articles published between 2014 and 2017*

| Verbal working memory | Cerebellar patients display mild to moderate VWM dysfunction, but not other types of working memory. The superior cerebellum is thought to be involved in the initiation of the motor sequence of phonological content during information encoding. At the same time, the inferior cerebellum is thought to support phonological storage during the maintenance of verbal information. | Silveri et al. (1998); Desmond et al. (1997); Levisohn et al. (2000); Riva & Giorgi (2000); Scott et al. (2001); Baddeley (2003); Steinlin et al. (2003); Gottwald et al. (2004); Justus et al. (2005); Hokkanen et al. (2006); Ravizza et al. (2006); Ben-Yehudah et al. (2007); Ziemus et al. (2007); Chiricozzi et al. (2008); De Ribaupierre et al. (2008); Kirschen et al. (2008); Vaquero et al. (2008); Stoodley & Schmahmann (2009); Kirschen et al. (2010); Marvel & Desmond (2010); Law et al. (2011); Cooper et al. (2012); Marvel & Desmond (2012); Macher et al. (2014) |
| Writing | Neural network subserving handwriting skills include the language dominant superior parietal region, the dorsolateral and medial premotor cortex and the thalamus. Recent studies also conclude that the anterior lobe of the right cerebellum is important for the execution of fine finger movement necessary for writing. Hypoperfusion is recorded in agraphia cases after cerebellar lesions; it is evident in both the cerebellum and unaffected cortical regions implicated in writing. | Haggard et al. (1994); Marien et al. (1996); Fabbro et al. (2000); Marien et al. (2001); Moretti et al. (2002); Fabbro et al. (2004); Marien et al. (2007); Marien et al. (2008); De Smet et al. (2011); Marien et al. (2013); Borkowska et al. (2014); van Gaalen et al. (2014) |
Summary of the available evidence on the cerebellar involvement in different aspects of language, based on (Marien et al., 2014) and articles published between 2014 and 2017*

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reading</strong></td>
<td>The cerebellum plays different roles during the different stages of learning to read. For beginner readers it is important for the automatisation of grapheme-phoneme conversion, while for the more skilled readers it is important for the internalisation of speech important for silent reading.</td>
<td>Fulbright et al. (1999); Vlachos et al. (2007); Ben-Yehudah &amp; Fiez (2008); Strick et al. (2009); Khelifa-Gallios et al. (2015); Travis et al. (2015).</td>
</tr>
<tr>
<td><strong>Motor regulation of speech</strong></td>
<td>The cerebellum receives input from BA44 (Broca’s area) via the left anterior insula, and then projects to the primary motor cortex via the left ventral premotor cortex. Apraxia of Speech (AOS) is the speech motor planning disorder that results from damage to the cortical areas of the speech production network. Ataxic dysarthria (AD) is the speech execution disorder that results from cerebella lesions of the speech production networks. Common features of AD (but not AOS) are respiratory and phonatory impairments.</td>
<td>Ziegler &amp; Wessel (1996); Ziegler (2002); Marien et al. (2006); Marien et al. (2007); Ackermann (2008); Eickhoff et al. (2009); Manto et al. (2012); Poretti et al. (2014)</td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td>Verbal fluency is often impaired in cerebellar patients, and phonological fluency seems to be more affected than semantic fluency. Data on cerebellar function in verbal fluency support the hypothesis that sequencing processing is the basic function of the cerebellum in language.</td>
<td>Leggio et al. (2000); Brandt et al. (2004); Richter et al. (2007); Schweizer et al. (2008); Schweizer et al. (2010); Arasanz et al. (2012); Peterburs et al. (2012)</td>
</tr>
</tbody>
</table>

* Studies published between 2014 and 2017 were identified by searching PubMed database using associated key terms; no further selection criteria were applied.
3.1.4 Functional topography of the ‘linguistic’ cerebellum

The topography for the motor and cognitive functions of the cerebellum is well-described (Stoodley & Schmahmann, 2010). Specifically, the anterior lobe, extending into medial lobule VI and lobule VIII, facilitates sensorimotor modulation. At the same time, Lobules VI and VII, connected to the paralimbic and association cortices, are important for cognition and emotions (Figure 3.5). This distinction seems to extend to language; different cerebellar structures are involved in the motor control of the oral-pharyngeal-vocal apparatus for speech production and higher-order semantic, phonemic and syntactic processing of language (Marien et al., 2014).

Evidence suggests that overt speech is mediated by the vermal and paravermal regions of lobules V-VI and VII-VIII, which are areas linked to the sensorimotor areas of the cerebral cortex. Slowed speech and dysarthria are associated with damage to vermal and paravermal lobules V and VI and midline lobules VIIAf, VIIB and VIIIa (Ackermann, Vogel, Petersen, & Poremba, 1992; Grodd, Hulsmann, Lotze, Wildgruber, & Erb, 2001; Urban et al., 2003; Schoch, Dimitrova, Gizewski, & Timmann, 2006).

Language functions not dependent on motor processing, such as lexical access, comprehension, phonological and semantic processing and reading, are associated with the right posterior-lateral cerebellum, involving lateral lobules VI and VII (Crus I and II), which are reciprocally linked to the
language networks of the cerebral cortex (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; Jansen et al., 2005; Stoodley & Schmahmann, 2009).

Finally, lesion studies indicate that damage to the right Crus II results in verbal fluency impairment, whereas damage to the paravermal regions in lobules VII, VII and VIII A results in slower speech. Impaired verbal fluency and agrammatism are described following damage to the cerebellar posterior lobe, often, but not always, from lesions to the right hemisphere (Richter et al., 2007; Flippi et al., 2011).

In addition to the cerebellar cortex, the dentate nucleus, located within the cerebellar white matter, has been implicated in cognitive and language functions. Similar to the cerebellar cortex, there seems to be a topographic division when it comes to the specialisation of the motor and non-motor linguistic functions of the dentate nucleus (Dum & Strick, 2003). Activation within the right lateral cerebellum and ventrocaudal part of the right dentate nucleus have been reported during verb generation tasks (Thurling et al., 2011). The paravermal and rostral parts of the dentate nucleus bilateral activation have been reported in speech articulation tasks (Marvel & Desmond, 2010). In-vivo studying of the deep cerebellar nuclei remains a challenge due to difficulties with spatially resolving these very small structures with conventional imaging techniques, such as MRI.
Chapter 3

Figure 3.5. Cerebellar anatomy showing major fissures, lobes, and lobules. Red – anterior lobe, lobules I-V; cream - posterior lobe, lobules VI-IX, purple - flocculonodular lobe, lobule X. Lobule VII is subdivided into Crus I, Crus II, and VIIB in the hemispheres, and VIIAf, VIIAt, and VIIB in the vermis. Lobule VIII is subdivided into VIIIA and VIIIB. From (D’Mello & Stoodley, 2015. Figure courtesy of Professor Jeremy Schmahmann).

3.1.5 Elevated risk of language impairments in PFT survivors

Summarising the discussion so far, a normally developing central nervous system, including the cerebellum, is a necessary neuroanatomical mechanism to facilitate the acquisition of language. In addition, sufficient and timely external stimulation is required in the form of social interactions and schooling for normal linguistic development to occur. From this perspective, paediatric posterior fossa tumour patients face an increased risk of developing language deficits. On one hand, tumour growth, resection and adjuvant treatment are likely to disrupt the cerebello-cerebral neural
pathways that are crucial for language processing at the CNS level. On the other hand, prolonged periods of hospitalisation and treatment are likely to deprive these children of normal social and educational experiences and limit their communication opportunities, which are important for healthy language acquisition (Brinkman et al., 2012).

As demonstrated in the literature review (Chapter 2), so far studies of long-term linguistic deficits in PFT survivors have been largely inconsistent in terms of both their methodological approaches and findings. Very few studies have focused on a detailed investigation of language skills (Hudson and Murdoch, 1992; Richter et al., 2005; Huber, Bradley, Spiegler, & Dennis, 2007; Morgan et al., 2011). Instead, where linguistic abilities have been examined, this has been predominantly in the context of general cognitive profiling.

There is clearly a need to investigate language deficits with more rigour in this group of patients, both to improve the understanding of the depth and scope of the problem, and to propose ways to support rehabilitation. The relationship between linguistic skills, non-verbal cognitive abilities and motor deficits must also be examined, but without the a-priori assumption that language abilities are fully dependent on the other two sets of skills.

### 3.1.6 Aims and hypotheses

The present study investigates the hypothesis that posterior fossa tumours sustained in childhood will lead to long-term language deficits, through the detailed neuropsychological assessment of PFT patients and comparison to a matched healthy control group. Several aims were pursued: to conduct the most detailed neuropsychological investigation
of the language skills in this group of patients to date,
- to use a novel statistical analysis approach to establish which linguistic skills are affected most prominently and whether any strengths are retained,
- to assess how non-verbal intelligence and manual dexterity skills relate to language performance,
- to assess the effect of age on language performance.

3.2 Method

3.2.1 Participant recruitment

NUH paediatric neuro-oncology records dating back to 1992 were examined in order to identify eligible participants for the study. The eligibility criteria were i) PFT sustained before the age of 16 years, ii) at least 12-months post-surgery, iii) aged between 16 years 0 months and 21 years 11 months at the time of participation, iv) English as the primary language of schooling from the age of at least 11 years, and v) capacity to consent. 48 eligible participants were identified and sent an introductory letter with the study information sheet enclosed (Appendix 4), using the postal address from the NUH patient database. A reminder letter was sent six months later to those patients who had not responded to the first recruitment letter.

For the healthy control recruitment, the inclusion criteria were: i) aged between 16 years 0 months and 21 years 11 months at the time of participation, ii) English as the primary language of schooling from the age of at least 11 years, iii) capacity to consent, and iv) no history of cancer, or neurological, psychiatric or developmental disorders. The preferred recruitment strategy was to identify volunteers by asking patients to invite a friend or a sibling close in age and
of the same gender in order to achieve the best socioeconomic background matching. Research shows that intellectual and linguistic development is affected by children’s socioeconomic background (Wells, 1981; Dickinson & Snow, 1987). However, only one healthy volunteer could be recruited using this strategy. The remaining healthy volunteers were recruited by contacting local colleges and universities. The healthy volunteers and patients were group-matched by gender, age and social background, using the Index of Deprivation Affecting Children (IDACI).

Informed consent was sought from all of the participants directly since they were all over the age of 16 and had the capacity to consent. For the majority of the patients, however, consent was also sought from their parents or guardians who were present during the testing sessions. Prior to the commencement of the first assessment session all of the participants signed and dated consent forms, were given sufficient time to ask questions and were informed of their right to withdraw at any time. All of the participants received £50 reimbursement in shopping vouchers.

### 3.2.2 Collection of the clinical information

The patients’ electronic and paper records were accessed to collect the clinical information relevant to the study. This included the date of surgery, tumour type, size and location, extent or resection, any adjuvant treatment received subsequent to the surgery, radiotherapy dose, chemotherapy drug, and presence and duration of post-operative mutism. This information was available for the majority of the participants although there were some missing values. Other relevant variables were considered such as the duration of
symptoms prior to diagnosis, pre-operative ataxia, pre- and post-operative hydrocephalus and surgical approach.

3.2.3 Assessments

3.2.3.1 Language ability: Clinical Evaluation of Language Fundamentals, 5th edition

Language was assessed using the Clinical Evaluation of Language Fundamentals battery, 5th edition (Wiig et al., 2013). This comprehensive test battery, first published in 1980, allows the identification of language strengths and weaknesses. The battery was last standardised in 2012 with over 3000 English-speaking children and young adults in the USA. Out of these, there were 330 participants between the ages of 16:0 and 21.11, the age group relevant to the current study. The CELF-5 battery has also been validated with several clinical groups, including 166 individuals with the diagnosis of a language disorder, with high levels of internal consistency and reliability (Wiig et al., 2013).

The CELF-5 battery is comprised of a range of short tests and activities. For the age group of the present study, it offers ten practical tests (Word Classes, Following Directions, Formulated Sentences, Recalling Sentences, Understanding Spoken Paragraphs, Word Definitions, Sentence Assembly, Semantic Relationships, Reading Comprehension and Structure Writing), two rating scales based on the feedback from parents and/or teachers (Pragmatics Profile and Observational Rating Scale) and one interaction-based checklist (Pragmatics Activities Checklist). Only ten core tests were administered in the current study as they were sufficient for the calculation of the composite scores and analyses of the
specific language functions. The Pragmatics Profile and Observational Rating Scales were omitted as they required extensive input from the teachers and parents, which was beyond the remit of the present study. The Pragmatics Activities Checklist was not completed due to the time constraints of the already lengthy assessment sessions and the requirement of a range of additional material resources (e.g. shared snacks, craft materials). Table 3.2. presents the description of all of the tests administered in the present study. The administration and scoring were performed in accordance with the CELF-5 manual administration manual. The raw test scores were calculated by adding the item scores. Using age-appropriate tables in the administration manual, each raw test score was converted into a norm-referenced scaled score. Scaled scores are useful for comparing a student's performance with the typical performance of the same age group in the normative sample. They are plotted on a normalised scale with a mean of 10 and standard deviation of 3. Thus, scores between 7 and 13 encompass the average range for a given age group.

Composite scores reflect abilities in several language skill areas. These were calculated by adding the component scaled scores (Figure 3.6) and converting the sum into a norm-referenced standard score, again using age-appropriate tables in the manual. All of the composite scores were plotted on a normalised standard score scale with a mean of 100 and a standard deviation of 15. Consequently, composite scores of between 85 and 115 reflect the average range of performance in a skill area for a given age group (Figure 3.7).
3.2.3.2 Non-verbal intelligence: Raven’s Progressive Matrices

Non-verbal intelligence was assessed using Standard Raven’s Progressive Matrices test, plus version (Raven, 2008). This measure was selected as it has minimal reliance on linguistic abilities beyond understanding the instructions of the administrator, and thus can serve as a control measure of non-verbal intelligence. The test consists of 60 multiple choice items of progressively increasing difficulty, presented in 5 sets, with 12 items per set. Participants are asked to identify a missing element that completes the pattern (see Figure 3.8 for an example). The typical completion time varied between 30 and 60 minutes. The raw score was calculated by adding the individual scores for all of the correctly completed patterns. This was then converted into a norm-referenced standard score, using age-appropriate tables in the manual.
<table>
<thead>
<tr>
<th>Test</th>
<th>Task performed</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Word Classes</strong></td>
<td>The student chooses two of four orally presented words that are related</td>
<td>To evaluate the student’s ability to understand relationships between words on semantic class features, function or place or time of occurrence</td>
</tr>
<tr>
<td><strong>Following Directions</strong></td>
<td>The student points to shapes in the stimulus book in response to oral directions of increasing length and complexity</td>
<td>To evaluate the student’s ability to a) interpret spoken directions of increasing length and complexity; b) follow the stated order of mention of familiar shapes with varying characteristics such as colour, size or location; and c) identify from several choices the pictured objects that were mentioned. These abilities reflect short-term and procedural memory capacities</td>
</tr>
<tr>
<td><strong>Formulated Sentences</strong></td>
<td>Using a visual stimulus as a reference, the student formulates a sentence about the picture using one or two targeted words presented orally by the examiner</td>
<td>To evaluate the student’s ability to formulate complete, semantically and grammatically correct, spoken sentences of increasing length and complexity (i.e. simple, compound, and complex sentences), using given words (e.g., car, if, because) and contextual constraints imposed by illustrations. These abilities reflect the capacity to integrate semantic, syntactic, and pragmatic rules and constraints while using working memory</td>
</tr>
</tbody>
</table>
Table 3.2 (Continued)

**CELF-5 tests administered as part of the present study, based on CELF-5 examiner’s manual (Wiig et al., 2013)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Task performed</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recalling Sentences</td>
<td>The student imitates sentences presented orally by the examiner</td>
<td>To evaluate the student’s ability to listen to spoken sentences of increasing length and complexity, and repeat the sentences without changing word meaning and content, word structure (morphology), or sentence structure (syntax). Semantic, morphological and syntactic competence facilitates immediate recall (short-term memory)</td>
</tr>
<tr>
<td>Understanding Spoken Paragraphs</td>
<td>The student responds to questions about a paragraph presented orally by the examiner. The questions target the paragraph’s main idea, details, and sequencing, as well as inferential and predictive information</td>
<td>To evaluate the student’s ability to a) sustain attention and focus while listening to spoken paragraphs, b) create meaning from oral narratives and text, c) answer questions about the content of the information given, and d) use critical thinking strategies for interpreting beyond the given information. The questions probe for an understanding of the main idea, memory for facts and details, recall of event sequences, and making inferences and predictions</td>
</tr>
<tr>
<td>Word Definitions</td>
<td>The student defines a word that is named and used in a sentence</td>
<td>To evaluate the student’s ability to a) analyse words for their meaning features, b) define words by referring to class relationships and shared meanings, and c) describe meanings that are unique to reference or instance</td>
</tr>
</tbody>
</table>
Table 3.2 (Continued)

*CELF-5 tests administered as part of the present study, based on CELF-5 examiner's manual (Wiig et al., 2013)*

<table>
<thead>
<tr>
<th>Test</th>
<th>Task performed</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentence Assembly</td>
<td>The student produces two semantically and grammatically correct sentences from words or groups of words presented visually and orally by the examiner</td>
<td>To evaluate the student’s ability to formulate grammatically-acceptable and semantically-meaningful sentences by manipulating and transforming given words and word groups</td>
</tr>
<tr>
<td>Semantic Relationships</td>
<td>After listening to a sentence, the student selects the two correct choices from four visually and orally presented options that answer a target question</td>
<td>To evaluate the student’s ability to interpret sentences that a) make comparisons, b) identify location or direction, c) specify time relationships, d) include serial order, or e) are expressed in a passive voice</td>
</tr>
<tr>
<td>Reading Comprehension</td>
<td>The student responds to orally presented questions about passages he or she reads. The questions target the paragraph’s main idea, details, and sequencing, as well as inferential and predictive information</td>
<td>To evaluate the student’s ability to a) sustain attention and focus while reading paragraphs of increasing length and complexity, b) create meaning from written narratives and text, c) answer questions about the content of the information given, and d) use critical thinking strategies to interpret beyond the given information. The questions probe for understanding of the main idea, memory for facts and details, recall of event sequences, and making inferences and predictions</td>
</tr>
<tr>
<td>Structured Writing</td>
<td>The student writes a short story by completing a sentence and writes one or more additional sentences</td>
<td>To evaluate the student’s ability to use situational information given by a story title, an introductory sentence, and an incomplete sentence to create and write a thematic, structured narrative</td>
</tr>
</tbody>
</table>
Figure 3.6. Structure of the CELF-5 assessment battery
Figure 3.7. The normal curve with standard scores, scaled scores and percentile ranks
3.2.3.3 Visuo-motor coordination: Purdue Pegboard Test

Visually-guided fine manual control skills were measured using the Purdue Pegboard test (Tiffin, 1948), which is widely used in clinical research. The test kit contains a wooden board with a set of pins, washers and collars (Figure 3.9). Participants are required to complete four timed tests where they place the pins into the pegboard. Tasks one and two require one hand only, first dominant, then non-dominant. Task three is a two-handed task where both hands perform synchronous actions. In tasks one, two and three only pins are used. Task four also involves both hands, which perform different successive actions using a range of parts. The Purdue Pegboard test in not norm-referenced, so only raw scores are calculated based on the number parts used during each task within a given time frame (30 seconds for tasks one, two and three, and 60 seconds for task four).
3.2.4 Procedure

Overall, the study participation required two visits, one for the neuropsychological assessment, and then the second, within several weeks, for the neuroimaging assessment, discussed in Chapters 4 and 5 of this thesis. For the first visit, participants who were deemed eligible were invited to visit the School of Psychology or Queen’s Medical Centre at the University of Nottingham at a mutually convenient time. The assessment was carried out by the Principal Investigator (PhD student) in a quiet room, and lasted up to four hours, including breaks. See Table 3.3 for a summary of the Visit 1 schedule. Both the patients and the healthy controls completed the Clinical Evaluation of Language Fundamentals, 5h edition, Raven's Progressive Matrices and Purdue Pegboard test batteries. In addition, the patients also completed the Frenchay Dysarthria Assessment, discussed in Chapter 6. The Method section of Chapter 4 contains details of the Visit 2 schedule. The full study protocol can be found in Appendix 1.
Table 3.3  
**Neuropsychological assessment: Visit 1 schedule**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Purpose</th>
<th>Time required (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting up</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>CELF-5 battery</td>
<td>To measure language skills</td>
<td>60-80 minutes</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Raven's Progressive Matrices</td>
<td>To measure non-verbal cognitive abilities</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Purdue pegboard tests</td>
<td>To measure manual dexterity and visuo-motor coordination</td>
<td>10-20 minutes</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>The Frenchay Dysarthria Assessment (patients only)</td>
<td>To measure motor speech functioning</td>
<td>20-30 minutes</td>
</tr>
<tr>
<td>Total visit time</td>
<td></td>
<td>2 hours 40 minutes - 3 hours 50 minutes</td>
</tr>
</tbody>
</table>

### 3.2.5 Statistical analyses

The primary objective of the data analyses was to quantify the functional differences between the patients and healthy controls. This was achieved by applying multivariate analysis for integrated assessment of the differences in multiple domains simultaneously, followed by the univariate analyses for more detailed consideration of the functional differences in specific domains. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 22, Chicago, Il, USA).

#### 3.2.5.1 Multivariate analysis of variance (MANOVA)

MANOVA was performed as a first step. One of the main advantages of applying MANOVA instead of several between-group comparison tests is that it reduces the chances of inflating the familywise error rate (Field, 2013). If MANOVA produces a statistically significant result, post-hoc tests are then performed to establish the precise source of the
differences. In addition, MANOVA allows the examination of the individual contribution of the dependent variables to any observed between-group differences, using discriminant function analyses. Discriminant function coefficient values ranging between 0 and 1 reflect the amount of the contribution of the individual variables to the overall inter-group differences. MANOVA is considered to have greater power compared to univariate procedures such as ANOVA, because it takes into account correlations between the dependent variables (Huberty & Morris, 1989). The amount of power achieved can vary depending on the magnitude of the expected effect size and directionality of the between-group difference (Cole, Maxwell, Arvey, & Salas, 1994; Field, 2013). In the present study, we expected to observe large effect sizes and differences in the same direction (i.e. all of the patients' scores would be lower compared to the healthy controls). If these conditions were satisfied, the MANOVA could be considered an appropriate and sufficiently powerful procedure.

3.2.5.2 Univariate analyses

Following the multivariate analysis of variance, univariate tests were applied for the detailed analyses of differences in performance on various measures. Where the data met the assumptions for parametric tests, Student's t-tests were used (CELF-5 scaled scores, CELF-5 core and index scores, PPB assembly score, RPM standard score). For non-normally distributed data (PPB one-hand and two-hand scores) the Mann-Whitney U-test was used. Bonferroni familywise error correction was applied where appropriate. In addition to the p-values, effect sizes were calculated for all reported differences in order to achieve the best possible level of understanding of
the differences from both the statistical and clinical perspectives.

Besides the direct performance score comparisons, correlational analyses were applied to assess the degree of association between performance on different measures. Bivariate Pearson's $r$ tests were used to report the association between the CELF-5 test scaled scores, manual dexterity and non-verbal intelligence. To isolate the effect of age on the association between language and non-verbal intelligence, partial correlation was applied. Finally, Fisher's $z$-transformation was used to assess whether language/nonverbal intelligence association was statistically different between the patients and healthy controls both before and after age correction.

Finally, the degree of variability in the individual language profiles was assessed using a derived measure, the coefficient of variation, and compared between the groups using the Student's t-test. Quantification of the variability in the individual functional profiles is important for understanding whether all language functions are affected uniformly by the disease. Increased homogeneity of the individual patients' linguistic profiles would imply that PFT promotes the convergence of all language functions at a similar level in the long-term recovery phase, while increased heterogeneity would indicate that specific language functions are affected differently by the tumour and its treatment.

### 3.3 Results

#### 3.3.1 Participant characteristics

Fourty-eight eligible patients were identified from the
Nottingham University Hospitals patient database and invited to participate in the study. Patients were contacted directly as all of them were over 16 years of age and could consent for themselves. Twenty-one patients expressed an interest and were recruited for the study. Healthy volunteers were recruited from the Nottingham area by contacting local high schools and universities and group-matched to the patients on a number of measures. A summary of the demographic characteristics of the participating patients and healthy volunteers is available in Table 3.4. The clinical characteristics of the patients are summarised in Table 3.5.

Using the G*Power 3.9.1 software (Faul, Erdfelder, Lang & Buchner, 2007), it was determined that with the total obtained sample size of 43, the study had 65% power to detect a moderate effect size of .3, and 95% power to detect a large effect size of .5, assuming a one-tailed hypothesis and critical significance level of .05. In clinical studies, 80% power is frequently cited as an acceptable threshold (Suresh & Chandrashekar, 2012). Thus, for the present study’s findings to be considered reliable, the achieved effect sizes had to be in the large range (above .5).

Table 3.4
Comparison of the demographic characteristics of the patients and healthy controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
<th>Healthy controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>21</td>
<td>22</td>
<td>.88</td>
</tr>
<tr>
<td>Age at assessment, Y:M, Mean (SD)</td>
<td>17:11 (1:8)</td>
<td>17:10 (1:1)</td>
<td>.80</td>
</tr>
<tr>
<td>Gender, F:M</td>
<td>13:8</td>
<td>14:8</td>
<td>.91</td>
</tr>
<tr>
<td>IDACI, Mean (SD)</td>
<td>.25 (.20)</td>
<td>.22 (.20)</td>
<td>.74</td>
</tr>
</tbody>
</table>

Note. *Number of participants that underwent neuropsychological assessment; some did not participate in the imaging arm of the study.
IDACI – The Income Deprivation Affecting Children Index
### Table 3.5

**Clinical characteristics of the patient sample**

<table>
<thead>
<tr>
<th>Patient study ID</th>
<th>Sex</th>
<th>Age at diagnosis*</th>
<th>Age at assessment*</th>
<th>Recovery time*</th>
<th>Tumour type</th>
<th>Tumour location</th>
<th>RT</th>
<th>ChT</th>
<th>Dominant hand</th>
<th>Mutism</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8</td>
<td>M</td>
<td>4:7</td>
<td>17:1</td>
<td>12:6</td>
<td>MB</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>R</td>
<td>Y</td>
</tr>
<tr>
<td>R8</td>
<td>F</td>
<td>4:2</td>
<td>16:4</td>
<td>12:4</td>
<td>MB</td>
<td>LC</td>
<td>Yes</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>D7</td>
<td>M</td>
<td>11:8</td>
<td>17:7</td>
<td>5:11</td>
<td>AC</td>
<td>4thV</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>E68</td>
<td>F</td>
<td>10:0</td>
<td>16:7</td>
<td>6:7</td>
<td>E</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>A8</td>
<td>F</td>
<td>8:6</td>
<td>16:11</td>
<td>8:5</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
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<tr>
<td>U8</td>
<td>F</td>
<td>11:10</td>
<td>16:2</td>
<td>4:4</td>
<td>HGG</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>E4</td>
<td>F</td>
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<td>20:11</td>
<td>4:11</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>C3</td>
<td>F</td>
<td>16:10</td>
<td>21:9</td>
<td>4:11</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>L6</td>
<td>F</td>
<td>16:7</td>
<td>18:10</td>
<td>2:3</td>
<td>AC</td>
<td>ML</td>
<td>No</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>C7</td>
<td>M</td>
<td>11:6</td>
<td>17:8</td>
<td>6:2</td>
<td>MB</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>N</td>
</tr>
<tr>
<td>S6</td>
<td>F</td>
<td>10:11</td>
<td>19:1</td>
<td>8:2</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>J7</td>
<td>M</td>
<td>1:0</td>
<td>17:3</td>
<td>16:3</td>
<td>MB</td>
<td>ML</td>
<td>No</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>S7</td>
<td>F</td>
<td>12:9</td>
<td>17:11</td>
<td>5:2</td>
<td>MB</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>Y</td>
</tr>
<tr>
<td>R7</td>
<td>M</td>
<td>6:6</td>
<td>18:9</td>
<td>12:3</td>
<td>MB</td>
<td>ML</td>
<td>Yes</td>
<td>Yes</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>S4</td>
<td>M</td>
<td>4:7</td>
<td>21:5</td>
<td>16:10</td>
<td>AC</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>Y</td>
</tr>
<tr>
<td>M48</td>
<td>M</td>
<td>5:1</td>
<td>17:6</td>
<td>12:5</td>
<td>AC</td>
<td>ML</td>
<td>No</td>
<td>No</td>
<td>L</td>
<td>N</td>
</tr>
<tr>
<td>A9</td>
<td>M</td>
<td>9:2</td>
<td>16:8</td>
<td>7:6</td>
<td>MB</td>
<td>ML</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>N</td>
</tr>
<tr>
<td>M78</td>
<td>F</td>
<td>8:0</td>
<td>17:3</td>
<td>9:3</td>
<td>E</td>
<td>4thV</td>
<td>Yes</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>E58</td>
<td>F</td>
<td>8:0</td>
<td>17:4</td>
<td>9:4</td>
<td>AC</td>
<td>BS</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>N</td>
</tr>
<tr>
<td>C9</td>
<td>F</td>
<td>11:6</td>
<td>16:7</td>
<td>5:1</td>
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<td>RC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>I9</td>
<td>F</td>
<td>7:9</td>
<td>16:8</td>
<td>8:11</td>
<td>AC</td>
<td>RC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>N</td>
</tr>
</tbody>
</table>

Mean (SD) - 9:5 (4:3)  17:11 (1:8)  8:6 (3:11)  -  -  -  -  -  -  -

3.3.2 MANOVA: Assessment of the between-group differences in language, non-verbal IQ and manual dexterity

One-way multivariate analysis of variance (MANOVA) was performed in order to examine the differences between the patients and healthy controls in terms of language performance, non-verbal IQ, and manual dexterity. Twelve dependent variables were examined in total, including ten CELF-5 scaled scores (language performance), RPM standard score (non-verbal IQ) and Purdue Pegboard assembly score (manual dexterity). The CELF-5 individual test scales scores were preferred over the CELF-5 index scores because MANOVA assumes independence of the DVs and this is upheld in the individual test scaled scores. Index scores, however, are composite measures with overlapping components, so they are not completely independent. In addition, several scaled scores are not included in the index score calculations, including Structured Writing, Word Definitions, and Reading Comprehension. Thus, using only index scores would omit some important aspects of language processing.

Initially, the relationships between the DVs were examined using Pearson correlations (Table 3.6) in order to test the assumption that there is at least moderate correlation between the DVs (Mayer, Gampst and Guarino, 2006). This assumption was satisfied with most of the correlation coefficients falling in the moderate range from $r = .3$ to $r = .7$. Weak correlations were observed between Sentence Assembly and the Recalling Sentences scaled scores ($r = .22$). Several correlations were above $r = .7$, but none of them exceeded $r = .76$, indicating that collinearity was not an issue (Field, 2013). Additionally,
a Box’s M value of 125.87 yielded a significance level of \( p = .26 \), suggesting equal covariance of matrices between the groups, and thus MANOVA was deemed appropriate. The one-way MANOVA revealed a statistically significant effect, Wilks’ \( \Lambda = .37 \), \( F(12, 30) = 4.32, p = .001 \), indicating that overall the performance of the patients differed significantly from that of the healthy controls on the functional assessments. The MANOVA was then followed up by a series of univariate ANOVA tests in order to establish specific measures that were contributing to the observed between-group differences.

Prior to the analyses, the homogeneity of variance was tested for all of the performance subscales. The variances for the Reading Comprehension Scaled Score were found to be non-homogenous (Levene’s test \( p < .05 \)). However, Howel (2009) suggests that MANOVA is still robust if none of the largest standard deviations is more than four times the size of the corresponding smallest, and this condition was satisfied (RCSS SD patients = 1.7, SD healthy controls = 3.3). The results revealed statistically significant differences between the groups for all of the measures investigated, except the Recalling Sentences Scaled Score, suggesting that only for this measure the groups did not differ in performance (Table 3.7).

In addition, discriminant function analyses were conducted in order to establish the proportion of individual contributions of each significant univariate F-test to the observed between-group functional differences. As there were two levels of the independent variable (Group), one eigenvalue and one
Table 3.6
**Pearson Correlation coefficient matrix for MANOVA variables**

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RPMSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 WCSS</td>
<td>.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 FDSS</td>
<td>.71</td>
<td>.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 FSSS</td>
<td>.44</td>
<td>.67</td>
<td>.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 RSSS</td>
<td>.40</td>
<td>.55</td>
<td>.67</td>
<td>.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 USPSS</td>
<td>.55</td>
<td>.68</td>
<td>.63</td>
<td>.76</td>
<td>.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 WDSS</td>
<td>.60</td>
<td>.74</td>
<td>.71</td>
<td>.66</td>
<td>.58</td>
<td>.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 SASS</td>
<td>.55</td>
<td>.55</td>
<td>.43</td>
<td>.42</td>
<td>.22</td>
<td>.58</td>
<td>.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 SRSS</td>
<td>.62</td>
<td>.71</td>
<td>.61</td>
<td>.65</td>
<td>.48</td>
<td>.71</td>
<td>.65</td>
<td>.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 RCSS</td>
<td>.54</td>
<td>.68</td>
<td>.55</td>
<td>.64</td>
<td>.49</td>
<td>.67</td>
<td>.64</td>
<td>.31</td>
<td>.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 SWSS</td>
<td>.62</td>
<td>.68</td>
<td>.55</td>
<td>.54</td>
<td>.33</td>
<td>.67</td>
<td>.68</td>
<td>.59</td>
<td>.66</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>12 PPAS</td>
<td>.60</td>
<td>.58</td>
<td>.60</td>
<td>.43</td>
<td>.42</td>
<td>.57</td>
<td>.64</td>
<td>.49</td>
<td>.55</td>
<td>.44</td>
<td>.59</td>
</tr>
</tbody>
</table>

Correlation is significant at the 0.01 level (2-tailed)

Correlation is significant at the 0.05 level (2-tailed)

**Note.** RPMSS – Raven’s Progressive Matrices standard score, WCSS – Word Classes scaled score, FDSS – Following Directions scaled score, FSSS – Formulated Sentences scaled score, RSSS – Recalling Sentences scaled score, USPSS – Formulated Sentences scaled score, WDSS – Word Definitions scaled score, SASS – Sentence Assembly scaled score, SRSS – Semantic Relationships scaled score, RCSS – Reading Comprehension scaled score, SWSS – Structured Writing scaled score, PPAS – Purdue Pegboard Assembly score

Canonical correlation were extracted by the MANOVA. Thus the eigenvalue of 1.73 accounted for 100% of the model variance. The canonical correlation associated with the eigenvalue was equal to .80, indicating that 63.4% of the variance in the discriminant function derived score was accounted for by group membership.

The analysis of the standardised discriminant function coefficients revealed that the groups were differentiated by a canonical variate with the greatest weighting coming from the Purdue pegboard assembly score (.84) followed by the Semantic Relationship scaled score (.62), the Reading Comprehension scaled score (.59), and the Word Definition scaled score (.45). These are, therefore, the functional dimensions where the patients’ underperformance was most marked compared to that of the healthy controls.
Table 3.7
Univariate analyses of the performance differences between the patients and healthy controls on individual language tests, non-verbal IQ and manual dexterity

<table>
<thead>
<tr>
<th>Measure</th>
<th>M (SD)</th>
<th>F</th>
<th>p</th>
<th>Effect size, Glass’s Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients N = 21</td>
</tr>
<tr>
<td>RPMSS</td>
<td>85.00</td>
<td>104.09 (15.93)</td>
<td>13.69</td>
<td>.001</td>
</tr>
<tr>
<td>WCSS</td>
<td>7.57 (3.03)</td>
<td>10.36 (2.36)</td>
<td>11.44</td>
<td>.002</td>
</tr>
<tr>
<td>FDSS</td>
<td>8.86 (2.85)</td>
<td>10.86 (2.49)</td>
<td>6.05</td>
<td>.018</td>
</tr>
<tr>
<td>FSSS</td>
<td>8.48 (2.80)</td>
<td>11.00 (2.41)</td>
<td>10.05</td>
<td>.003</td>
</tr>
<tr>
<td>RSSS</td>
<td>9.76 (2.34)</td>
<td>10.27 (2.07)</td>
<td>.57</td>
<td>.453</td>
</tr>
<tr>
<td>USPSS</td>
<td>7.29 (2.92)</td>
<td>10.32 (2.75)</td>
<td>12.31</td>
<td>.001</td>
</tr>
<tr>
<td>WDSS</td>
<td>8.67 (3.07)</td>
<td>13.09 (3.61)</td>
<td>18.64</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>SASS</td>
<td>7.76 (2.90)</td>
<td>10.00 (2.23)</td>
<td>8.11</td>
<td>.007</td>
</tr>
<tr>
<td>SRSS</td>
<td>10.19 (3.42)</td>
<td>12.64 (2.34)</td>
<td>7.57</td>
<td>.009</td>
</tr>
<tr>
<td>RCSS</td>
<td>7.29 (3.30)</td>
<td>10.09 (1.69)</td>
<td>12.55</td>
<td>.002</td>
</tr>
<tr>
<td>SWSS</td>
<td>6.15 (4.12)*</td>
<td>11.77 (4.06)</td>
<td>20.89</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PPAS</td>
<td>24.38 (9.16)</td>
<td>37.64 (6.02)</td>
<td>31.75</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>Healthy Controls N = 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPMSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USPSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WDSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SASS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. RPMSS – Raven’s Progressive Matrices standard score, WCSS – Word Classes scaled score, FDSS – Following Directions scaled score, FSSS – Formulated Sentences scaled score, RSSS – Recalling Sentences scaled score, USPSS – Understanding Spoken Paragraphs scaled score, WDSS – Word Definitions scaled score, SASS – Sentence Assembly scaled score, SWSS – Semantic Relationships scaled score, RCSS – Reading Comprehension scaled score, PPAS – Purdue Pegboard Assembly score
p-values uncorrected
Effect size $Δ = (M_{healthy controls} - M_{patients}) / SD_{healthy controls}$
*One patient excluded due to severe visual impairment

Somewhat less, although still a substantial amount, of weighting was observed from the Following Directions scaled score (.34), Raven Progressive Matrices standard score (.30), and Structured writing scaled score (.22). A minimal contribution was observed from the Word Classes scaled score (-.09), Sentence Assembly scaled score (.09), Understanding spoken paragraphs scaled score (-.08), and Formulated sentences scaled score (-.08). The Recalling Sentences scaled score was not found to contribute significantly to the between-group differences, and thus its discriminant function coefficient was not analysed (Table 3.8).
In order to estimate the group centroids (canonically derived group means), all of the scores (except for the Recalling Sentences score, where there was not a significant group difference) were multiplied by the corresponding unstandardised discriminant function coefficients and then summed across the groups.

The sampling distribution for the data derived from the multivariate analyses was different from the sampling distribution of the univariate data, so an independent sample Student’s t-test was performed using values of the canonically derived centroids as the dependent variable and group belonging as a fixed factor, with a stringent statistical significance level of $p = .001$ to maximise confidence in the observed results (Neufeld & Garner, 1990). The results revealed that there was a lower centroid value in the patients ($M = 4.47, SD = 1.46$) compared to the healthy controls ($M = 7.18, SD = .96$), $t(41) = 7.23$, $p < .001$, Cohen’s $d = 2.19$, confirming once again that patients’ overall performance on the behavioural measures was significantly poorer compared to the healthy controls.

**3.3.3 Language: CELF-5 composite scores**

As part of the MANOVA, univariate comparisons of the CELF-5 individual scaled test scores were performed and demonstrated that patients underperformed on all of the individual tests, except the Recalling Sentences Scaled Score (Table 3.7). In addition to the individual tests, the CELF-5 battery permits calculation of the Core Language Score (CLS) and four composite index scores: Language Content Index (LCI) Expressive Language Index (ELI), Receptive Language
Table 3.8

Discriminant function coefficients and their relationships with the canonical variable

<table>
<thead>
<tr>
<th>Measure</th>
<th>Discriminant function coefficients</th>
<th>Structure coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardised</td>
<td>Standardised</td>
</tr>
<tr>
<td>PPAS</td>
<td>-.11</td>
<td>-.84</td>
</tr>
<tr>
<td>SRSS</td>
<td>.21</td>
<td>.62</td>
</tr>
<tr>
<td>RCSS</td>
<td>-.23</td>
<td>-.59</td>
</tr>
<tr>
<td>WDSS</td>
<td>-.13</td>
<td>-.45</td>
</tr>
<tr>
<td>FDSS</td>
<td>.13</td>
<td>.34</td>
</tr>
<tr>
<td>RPMSS</td>
<td>-.02</td>
<td>-.30</td>
</tr>
<tr>
<td>SWSS</td>
<td>-.05</td>
<td>-.22</td>
</tr>
<tr>
<td>WCSS</td>
<td>-.03</td>
<td>-.09</td>
</tr>
<tr>
<td>SASS</td>
<td>.03</td>
<td>.09</td>
</tr>
<tr>
<td>USPSS</td>
<td>-.03</td>
<td>-.08</td>
</tr>
<tr>
<td>FSSS</td>
<td>-.30</td>
<td>-.08</td>
</tr>
</tbody>
</table>

Note. Structure coefficients represent correlations between canonical and dependent variables

Note. RPMSS – Raven’s Progressive Matrices standard score, WCSS – Word Classes scaled score, FDSS – Following Directions scaled score, FSSS – Formulated Sentences scaled score, USPSS – Understanding Spoken Paragraphs scaled score, WDSS – Word Definitions scaled score, SASS – Sentence Assembly scaled score, SRSS – Semantic Relationships scaled score, RCSS – Reading Comprehension scaled score, SWSS - Structured Writing scaled score, PPAS – Purdue Pegboard Assembly score

Index (RLI) and Language Memory Index (LMI). Each of these measures is calculated based on the selected individual test scores (see Methods).

The between-group performances on CLS, LCI, ELI, RLI and LMI were compared using a series of independent sample t-tests. Prior to conducting the t-test analyses assumptions of homogeneity of variance and normal distribution of data were tested. Levene’s tests demonstrated that the variances between the groups were not significantly different for all of the composite scores (all p > .05). Shapiro-Wilk tests indicated that the distribution of the data was not significantly different from normal for all of the composite scores (all p > .05). Thus, the assumptions for the parametric analyses were upheld and,
t-tests were deemed appropriate for the present data. The analyses revealed that the patients underperformed on all of the composite measures, compared to the controls, which was reflected by both the p-values and between-group effect sizes (Table 3.9)

**Table 3.9**
*Core Language and Index Scores in patients and healthy controls*

<table>
<thead>
<tr>
<th>Composite score, M (SD)</th>
<th>Patients, N = 21</th>
<th>Healthy controls, N = 22</th>
<th>t</th>
<th>p</th>
<th>Effect size, Glass’s Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLS</td>
<td>92.76 (15.58)</td>
<td>106.91 (12.83)</td>
<td>3.25</td>
<td>.002*</td>
<td>1.10</td>
</tr>
<tr>
<td>LCI</td>
<td>85.00 (14.64)</td>
<td>101.32 (12.50)</td>
<td>3.94</td>
<td>&lt;.001*</td>
<td>1.31</td>
</tr>
<tr>
<td>ELI</td>
<td>90.81 (10.16)</td>
<td>102.27 (10.27)</td>
<td>3.68</td>
<td>.001*</td>
<td>1.12</td>
</tr>
<tr>
<td>RLI</td>
<td>90.33 (15.93)</td>
<td>106.59 (13.09)</td>
<td>3.67</td>
<td>.001*</td>
<td>1.24</td>
</tr>
<tr>
<td>LMI</td>
<td>93.71 (18.85)</td>
<td>103.55 (10.92)</td>
<td>2.71</td>
<td>.01*</td>
<td>.90</td>
</tr>
</tbody>
</table>

*Significant after familywise error correction
Effect size $\Delta = (M_{\text{Healthy controls}} - M_{\text{Patients}}) / SD_{\text{Healthy controls}}$
CLS – Core Language Score, LCI – Language Content Index, ELI – Expressive Language Index, RLI – Receptive Language index, LMI – Language Memory Index

### 3.3.4 Variability in language profiles: coefficient of variation

Analyses of the language performance in the patients and healthy controls revealed an overall lower performance in language functioning for patients, based on the comparative analyses of the group means (Tables 3.7 and 3.9). One further important consideration is how much variability participants in both groups display in respect to their performance on different tests within the same neuropsychological battery; that is, whether the magnitude of the difference between the highest and lowest scores for the
patients is the same as for the healthy controls. Higher variability in the patient group would indicate that they display less uniform profiles compared to healthy controls in different sub-domains of language functioning. Notably, many of the patients displayed a gap of over three standard deviations between their lowest and highest scaled score, while for the healthy controls this difference appeared to be less pronounced and typically was within the range of 2 to 3 standard deviations.

To test whether this heterogeneity of language performance is statistically significant, a Coefficient of Variation measure (CoV) was calculated, using the following equation: \[ CV = \frac{SD}{M} \].

CoV was calculated for each participant based on the average scaled score obtained from the ten tests of the CELF-5 battery. The CoV values were normally distributed (Shapiro-Wilk test \( p > .05 \)); therefore an independent-sample t-test was considered appropriate for between-group comparisons. The equality of variances assumption was, however, violated (Levene’s test \( p = .001 \)), so an adjusted degrees of freedom value (df = 27.34) was used to assess the statistical significance. The analysis revealed that the variability in the patients' CELF-5 scaled scores was significantly greater than that for the healthy controls, implying greater heterogeneity in language profiles amongst the patients relative to the healthy controls. The results of the analysis are summarised in Table 3.10. Figure 3.10 provides a visual illustration of the variability in the language scores for the patients and healthy controls.
3.3.5 Manual dexterity assessment

Hand-eye coordination was the domain that accounted for the largest proportion of the between-group differences, according to the MANOVA. Only the Assembly Score was used in the multivariate analyses, as this was arguably the most informative measure of hand-eye coordination and fine motor skills in the battery. The univariate ANOVA demonstrated that the patients scored significantly lower on the assembly test compared to the controls (Table 3.7).

Other Purdue pegboard sub-tests included a single dominant hand test (DHT), a single non-dominant hand test (NHT), and a two-handed test (THT). Unlike the assembly tests, where the participants were required to use their hands in succession, with each hand performing a different operation, in the two-handed test, the patients performed simultaneous identical actions, demonstrating their ability to coordinate synchronous moves.
For the DHT, NHT and THT scores, the data were not normally distributed (all Shapiro-Wilk tests p < .05), and therefore non-parametric Mann-Whitney U-tests were performed. It was found that the patients’ performance was significantly poorer than that of the healthy controls on all three measures (Table 3.11).

### 3.3.6 Relationship between language and non-verbal intelligence

MANOVA discriminant function coefficient analyses revealed that the Raven’s Progressive Matrices performance contributed substantially to the between-group performance
Table 3.11
Patients’ and healthy controls’ Purdue Pegboard scores for the Dominant hand, Non-dominant hand and Two-handed tests

<table>
<thead>
<tr>
<th>PPB test score, Mdn (Range)</th>
<th>Patients, N = 21</th>
<th>Healthy controls, N= 22</th>
<th>U</th>
<th>p</th>
<th>Effect size, r</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHT</td>
<td>12 (5-17)</td>
<td>16 (13-17)</td>
<td>41.50</td>
<td>&lt;.001*</td>
<td>.71</td>
</tr>
<tr>
<td>NHT</td>
<td>11 (2-15)</td>
<td>14 (12-17)</td>
<td>52.50</td>
<td>&lt;.001*</td>
<td>.67</td>
</tr>
<tr>
<td>THT</td>
<td>8 (2-15)</td>
<td>12 (9-15)</td>
<td>56.00</td>
<td>&lt;.001*</td>
<td>.65</td>
</tr>
</tbody>
</table>

Mann-Whitney U-tests, one-tailed
* Significant after familywise error correction
Effect size $r = Z/\sqrt{N}$

differences and the mean non-verbal intelligence score of the patients was significantly lower than that of the healthy controls (Tables 3.7 and 3.8). It was also shown that the RPM standard scores correlated highly with the scaled scores on all of the individual language tests (Table 3.6).

In order to further examine the relationship between language ability and non-verbal intelligence, correlational analyses were performed to test the association between the RPM standard score and Core Language Score (CLS) as a summative measure of linguistic ability. This relationship is of interest as it can aid an understanding of whether non-verbal intelligence and language abilities are affected in a similar manner as a result of posterior fossa tumour.

The data for RPM and CLS were normally distributed (Shapiro-Wilk tests $p > .05$) with no outliers and a linear relationship between the variables. The homogeneity of variance assumption was also upheld (both Levene’s tests $p > .05$). Thus all of the conditions for the Pearson’s product moment
correlation were satisfied and this procedure was deemed appropriate. Initially, a simple bivariate correlation analysis was performed, followed by a partial correlation, controlling for age. Both the CLS and RPM standard scores were adjusted for the participants’ ages at the time of scoring, using the test manual. However, these adjustments lack specificity: all of the participants above the age of 17 years for CLS and above 16.5 years for RPM were assumed to fall into the same age group. In reality, a substantial difference in abilities may be present between, for example, a 17 and a 20-year old, especially after sustaining a brain tumour, which may alter the normal course of development.

Table 3.12 presents a summary of the analyses. There was a strong correlation between RPM and CLS, both before and after correction for age, which was statistically significant, at the time of testing, in the whole study sample. When analyses were conducted for each group separately, the correlation remained large and statistically significant for the healthy control group, both before and after the age correction. In the patient group, the correlation did not reach the familywise-corrected statistical significance threshold of $p = .02$; however, it remained at the borderline of the moderate to strong level. To test whether the strengths of the correlations between the two groups were significantly different, Fisher’s $r$-to-$z$ transformation was applied. The results demonstrated that both before and after the age correction, the correlation between CLS and RPM did not differ significantly for either the patients or the healthy controls (both $p > .05$). Thus, it can be concluded that the scores from each group form part of the same distribution and differ quantitatively, rather than
Table 3.12
Association between Core Language Score and Raven’s Progressive Matrices standard score in the whole sample and individual groups

<table>
<thead>
<tr>
<th>Model</th>
<th>Pearson’s correlation coefficient, r (p)</th>
<th>Fisher’s r-to-z transform, z (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample, N = 43</td>
<td>Bivariate: CLS/RPM</td>
<td>.62 (&lt; .001*)</td>
</tr>
<tr>
<td>Patients, N = 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy controls, N = 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Partial: CLS/RPM, controlling for age at the time of assessment</td>
<td>.62 (&lt; .001*)</td>
<td>.49 (.03)</td>
</tr>
</tbody>
</table>

*Significant after Bonferroni familywise error correction

CLS – Core Language Score, RPM – Raven’s Progressive Matrices

Qualitatively, from one another.

Figure 3.11 shows a plot of the CLS/RPM association and demonstrates that 48% of the patient scores fell below the normative mean on both measures whereas only 18% of the healthy control scores did. In comparison, 54% of the healthy control scores and only 10% of the patient scores fell above the normative sample mean on both measures. Clinically significant impairment is typically diagnosed when the assessment score falls below 2SD of the normative sample mean. In the CELF-5 and RPM test batteries this relates to a score of 70 or below. 24% of the patients demonstrated clinically significant impairment on at least one assessment measure, compared to none of the healthy controls. In other words, one in four patients were clinically impaired in terms of either language or non-verbal cognition, or both, indicating that childhood PFT is a serious risk factor for functional difficulties.
Chapter 3

Figure 3.11. Correlation plot of the association between the CLS and RPM standard scores, NM – normative mean, SD – standard deviation in a normative sample (1 SD = 15 score points). Filled circles – patients, hollow circles – healthy controls

3.4 Discussion

3.4.1 Constructing comprehensive functional profiles of the PFT survivors

In the present study, patients treated for a tumour to the posterior fossa during childhood and healthy controls were assessed on a broad battery of neuropsychological measures of language functioning, non-verbal intelligence, and manual dexterity in order to construct a comprehensive picture of their functional profiles post-cerebellar tumour and make inferences about any deviations from typical development. When a number of outcome measures are used for between-group comparisons, there is a much increased risk of false
positive error occurrence. Multivariate analysis of variance helps to overcome this limitation by allowing the calculation of a single canonical variable that can be compared between groups in order to establish whether or not those groups are functionally different overall (Field, 2013). Besides the familywise error protection aspect, this procedure is also informative when it comes to assessing the degree of association between different outcome variables, as this is a necessary prerequisite for running the multivariate procedure. Finally, and perhaps most importantly, it enables the calculation of discriminant function coefficients (DFCs) that tell us how much weight each outcome variable contributes to the inter-group differences (Enders, 2003).

Based on the multivariate analyses, the null hypothesis of no difference between the patients’ and healthy controls’ performance can be reliably rejected. The patients performed significantly less well overall compared to the controls. This type of integrated assessment of differences on a range of measures is rarely applied to clinical samples, as the objective of clinical research studies is often to isolate and pinpoint domain-specific impairments, predominantly for targeted treatment and rehabilitation. However, when a number of outcome measures are taken into account simultaneously, this provides the most comprehensive picture of a ‘real life’ functional profile. Arguably, the functional domains assessed in the present study (language, cognition and visuo-motor coordination) are utilised together in a variety of situations, such as play, educational, and social activities, making their integrated assessment highly relevant. Our findings support a large body of literature reporting post-cerebellar tumour deficits in a number of areas simultaneously. Recent reviews
have highlighted long-lasting adverse effects on working memory, executive functions, perception of time, speech disturbances, academic performance, and overall quality of life (Hanzlik, Woodrome, Abdel-Baki, Geller, & Elbabaa, 2015; Lassaletta, Bouffet, Mabbott, & Kulkarni, 2015). Reports from the ongoing longitudinal Child Cancer Survivor Study also stress that young adult-survivors of cancer, in particular those who have sustained medulloblastoma, face an elevated risk of multiple co-morbid deficits, including hearing impairment, stroke, lower educational attainment, depression, and anxiety (Prasad et al., 2015; King et al., 2016). Thus, multivariate approaches to the assessment of the functional profiles of PFT survivors, such as that used in a present study, offer a novel, comprehensive and integrated way of understanding the constellation of functional deficits in this patient group.

Further evidence for strong inter-dependency between linguistic abilities, intelligence, and manual dexterity comes from the correlational analyses reported in the present study. Mainly strong or moderate correlations were observed between all of the CELF-5 language scaled scores, the Purdue Pegboard assembly score, and the Raven’s Progressive matrices standard score. These notable associations are in agreement with the literature on typically developing children that suggests that cognitive development is highly linked to motor abilities (e.g. Davis, Pitchford, & Limback, 2011; Roebers et al., 2014). Although a recent systematic review stressed that the evidence for the link is currently inconclusive (van der Fels et al., 2014), the relationship certainly deserves further exploration, in view of its potential importance for the rehabilitation of this patient group. A growing body of
research is continuing to investigate the influence of fine and gross motor training on cognitive (e.g. Schellenber, 2004; Reed et al., 2010) and linguistic (e.g. Locatelly, Gatti, & Tettamanti, 2012; Yang, 2014) functions, with promising results. With sufficient evidence, this could be a powerful tool for the rehabilitation of PFT patients; by providing intensive motor skills training, cognitive and linguistics deficits may benefit indirectly and overall long-term functional outcomes could be improved.

The final aspect of the multivariate analyses was the assessment of discriminant function coefficients, which clarified key sources of the observed between-group differences reported here. The greatest contribution was observed from the Purdue Pegboard assembly test of manual dexterity, indicating that, out of all the domains assessed, this was the one where the patients demonstrated the most profound deficits compared to the controls. This finding is not surprising due to the cerebellum playing a pivotal role in the modulation of fine motor activities (for review see Manto et al. 2012). A separate sub-section of the present discussion is dedicated to the more detailed analyses of motoric deficits. The next three largest DFC values were obtained from the CELF-5 language tests of Semantic Relationships, Reading Comprehension and Word Definitions, indicating that, after manual dexterity, these were the three functions where the patients underperformed most prominently compared to the controls. Interestingly, all three tests assess higher-order language skills, such as the ability to understand spoken and written text, as well as vocabulary range and the ability to relay semantic information to a conversational partner through explaining the meaning of the words. The contributions of
these tests to inter-group differences were even larger than that associated with non-verbal intelligence. Considering that general cognitive impairment is one of the most robust findings in this group of patients (Robinson, Fraley, Pearson, Kuttlesch, & Compas, 2013; Lanzen, Mabbott, & Guger, 2015), this is an important observation, indicating that post-PFT patients may be at even greater risk of developing language deficiencies than non-verbal cognitive impairments. Several studies of long-term PFT survivors that simultaneously assessed aspects of language and cognition reported deficits in both (Edelstein et al., 2011; Vaquero, Gómez, Quintero, González-Rosa, & Márquez, 2008; Aarsen et al., 2004; Aarsen et al., 2009; Copeland, Moore, & Ater, 1999). However, none of the previous studies have compared the contribution of the different sets of abilities to the inter-group difference. In subsequent sections observed language deficits are considered in greater detail.

3.4.2 Long-term decline in language functioning following sustaining a PFT in childhood

The investigation of language functioning across the long-term recovery phase following a posterior fossa tumour was one of the primary aims of this investigation. Following the multivariate analysis, language deficits in specific domains were analysed in a more detailed manner using univariate procedures. It was hypothesised that language performance would be impaired in all domains in the patient sample compared to the healthy controls. The Clinical Evaluation of Language Fundamentals, 5th edition (Wiig, Semel, & Secord, 2013) was selected as one of the most comprehensive test batteries available in English that allows the assessment of strengths and weaknesses in language processing in children.
and young adults. For nine out of the ten test scaled scores and four composite language indices the null hypothesis of no difference could be reliably rejected based on the below-threshold critical significance values and large effect sizes.

Statistically significant poorer language abilities were shown in the patients compared to the controls on nine out of ten individual test scaled scores (Word Classes, Following Directions, Formulated Sentences, Understanding Spoken Paragraphs, Word Definitions, Sentence Assembly, Semantic Relationships, Structured Writing and Reading Comprehension) and all five composite index scores (Core Language Score, Language Content Index, Expressive language Index, Receptive Language Index and Language Memory Index). The key difference between the scaled and index scores is that the scaled scores provide performance information about the specific language function targeted by a particular test, while the composite scores reflect ability in a broader range of skill areas (Wiig et al., 2013). Each composite score is based on a sum of several scaled scores (Figure 3.6 of the Method section). These specific functions and skill areas are discussed further.

3.4.2.1 Deficits in specific language functions

The patients demonstrated a range of difficulties in regard to skills related to the semantic processing of language. The Word Classes test assessed their understanding of the relationships between words, such as whether the words belong to the same or different categories, or are related spatially or temporally, a skill crucial for both comprehension and the production of language (Honig, Diamond, Gutlohn, & Mahler, 2000). The Word Definitions test addressed how well a young person can access the broad, generic meanings
attached to individual words, beyond their contextually bound concrete meanings. Finally, the Semantic Relationships test measured their ability to interpret sentences that contain comparisons, time relationships and semantic order, which are often impaired in individuals with language disorders (Owens, 2013). As a group, the patients' average scores on all three tests were significantly lower than those of the healthy controls, indicating impairment in the important skill of semantic processing.

The Following Directions test assessed the skill of interpreting, recalling and executing oral directions of increasing length and complexity. Research has shown that difficulties in demonstrating this skill in and outside of the classroom may indicate an underlying language disorder (Tomlinson, 2014). This deficit can affect a variety of linguistically related tasks, such an understanding and following tasks according to specified sequences. The performance on this test was also diminished in the patient group.

Similarly, marked differences between the patients and healthy controls were observed on two tests that measured their ability to construct semantically and grammatically correct sentences using an available range of words (Sentence Assembly test) and within a given syntactic, semantic, and pragmatic context (Formulated Sentences test). Research suggests that students displaying difficulties with formulating more complex sentences (such as including adverbial, coordinate and subordinate clauses, embedded noun-phrase complements etc.) are likely to have difficulty with syntactic flexibility and be diagnosed with a language disorder (Nippold, Schwarz, & Undling, 1992).

In addition, the ability to interpret factual and inferential
information from a spoken and written extract was significantly poorer in the patients compared to the healthy controls, as assessed by the Understanding Spoken Paragraphs and Reading Comprehension tests. Being able to form a mental representation of a story and identify cause-effect relationships is crucial for its interpretation and subsequent recall (Norbury & Bishop, 2002; Karasinsky & Weismer, 2010). Although the Recalling Sentences test outcomes were not significantly different between the patients and the controls, impaired comprehension of information presented in audio and visual form is a significant concern, especially in the educational context.

Finally, all of the participants were also assessed on their ability to construct a story and relay its meaning in a written form, using the Structured Writing test. Research shows that writing a story may be even more challenging for a person with a language disorder, than telling it (Fey, Catts, Proctor-Williams, Tromblin, & Zhang, 2004). The outcomes of the test, once again, demonstrated significant under-performance in the patients compared to the controls.

It is important to note that the patients' test results can also be compared to normative data provided in the standardised assessments, as well as the scores generated by the group of healthy controls recruited to this study. When this evaluation was made, only the Structured Writing mean score for the patient group fell below one standard deviation from the normative mean, indicating a clinically significant impairment. The other test scores, although significantly different from the controls, were within the low average range of the standardised norms. In other words, in the absence of the control group, the patients' language performance on the vast
majority of tests would have been considered to be within the normal range. This highlights an important issue with neuropsychological assessments in general; the absence of a clinically diagnosed impairment does not mean that all functions are intact. If such a misjudgment is made in a clinical context, patients may not receive adequate diagnosis and rehabilitation. For this specific reason, neuropsychological observational research studies should ideally always recruit a healthy control group and the findings should be disseminated among clinicians to raise awareness of this potential discrepancy.

Interestingly, short-term verbal memory performance, assessed by a sentence recall test, was not found to differ significantly between the patients and the controls. The existent literature reports mixed findings in relation to working memory outcomes in PFT patients. Typically, working memory impairments are associated with sustaining a higher risk tumour and receiving adjuvant therapy (e.g. Konczak, Schoch, Dimitrova, Gizewski, & Timmann, 2005; Droit-Volet et al., 2013). In view of the small sample size recruited to this study and the significant differences found for all of the other tests between the group of patients and the healthy controls, this finding should be treated with caution and warrants further investigation.

3.4.2.2 Deficits in broader language skill areas

In order to construct a more comprehensive picture of the state of the participants' linguistic ability, composite index scores were also calculated, based on the summed individual test scores. Composite scores enable more specific description of a language disorder, should one be identified (Wiig et al.,
2013). It is, however, possible that a deficit will be detected in a specific language function, based on a low individual test score, but a language disorder will not be diagnosed because other normal test scores compensate for it. For this reason, it is important to evaluate both the test scores and the composite scores.

Just as with the individual test scores, composite scores can be compared to the normative and healthy controls’ data. In the present study, all of the average composite scores for the patients were significantly below the healthy controls' scores. However, compared to the normative data, they were mainly within the low average range (Core Language Score, Expressive Language Index, Receptive Language Index, Language Memory Index), with one composite score at the at-risk borderline level of one standard deviation below the normative mean (Language Content Index).

Core Language Score is a measure of general language ability, derived from the sum of the individual test scores that best distinguish normal from disordered language performance (Wiig et al., 2013). Thus, if a quick decision needs to be made regarding the presence of a language impairment, only the tests contributing to this index will be administered. The Receptive and Expressive Language Index scores assess the presence of a language disorder in the receptive (listening and auditory comprehension) and expressive domains respectively. This differentiation follows the long-standing tradition of separating the receptive and expressive language skill areas. However, a growing body of research suggests that such a differentiation is arbitrary and that a single-dimension model may better explain the nature of language disabilities (Tomblin & Zhang, 2006; Leonard, 2009). Language Memory Index is a measure of the ability to apply memory to language tasks. Although one of its component tests revealed no difference between the patients and the controls, nevertheless, the total index score was still significantly lower for the patient group than the control group.
Finally, the Language Content Index score was the lowest among all other composite scores in the patient group, suggesting notable difficulties in semantic development, such as concept and category development, the interpretation of factual and inferential information, vocabulary range and the ability to create meaningful semantically- and syntactically-correct sentences.

3.4.2.3 Increased heterogeneity of language profiles in PFT survivors

Besides near-global poor language abilities, the patients were also shown to have increased heterogeneity of performance in terms of linguistic functions compared to the controls. Put differently, the young people in the healthy control group displayed more uniform linguistic profiles than the patients, as the patients displayed a higher magnitude of difference between their highest and lowest scores on the different tests in the CELF-5 battery than was shown by the healthy controls. This finding is also in agreement with the evidence reported in the literature. However, for the first time we were able to demonstrate this effect statistically.

Typically, a higher degree of heterogeneity in the functional profiles of PFT survivors is evident from the reported values of a spread of scores around group means (e.g. Aarsen et al., 2004; Rueckriegel, Blankenburg, Henze, Baqué, & Driever, 2009; Janzen, Davie et al., 2010; Mabbott, & Guger, 2015). Besides confirming that language is a multi-faceted function, this also means that language difficulties are not necessarily global; each patient may retain certain strengths in specific areas, which can be utilised in intervention and education. The importance of the “peaky” cognitive profiles with more pronounced strengths and weaknesses must not be
underestimated. High discrepancy between performance in different domains can be a potential sign of atypical brain development. This can lead to numerous challenges for both patients on a practical functioning level, as well as professionals facilitating education and clinical support for those patients.

3.4.3. Stable relationship between language and non-verbal intelligence, unconfounded by the presence of the disease or age at assessment

In the present study, a detailed examination of the relationship between language and non-verbal cognitive skills was performed. A moderate to strong positive association was observed between the Raven’s Progressive matrices scores and all of the language scaled test scores. One reason for investigating this connection is the abundance of literature reporting diminished cognitive skills in PFT survivors. This is one of the most robust neuropsychological findings in this clinical population, in particular among patients that have received adjuvant therapy, as highlighted by several recent reviews of the literature (Wolfe, Madan-Swain, & Kana, 2012; Hanzlik, Woodrome, Abdel-Baki, Geller, & Elbabaa, 2015; Lassaletta et al., 2015). Thus, cognitive deficits may be regarded as a ‘reference point’, based on which the present clinical sample can be compared to the PFT population described in the published literature. As the prevalence and severity of the cognitive deficits in the present sample is in line with the published literature, it is plausible to suggest that the observed language deficits would also be typical for the PFT population.
Beyond the statistical relationship between these functional domains, there may be an even more close-knit connection between them. Indeed, a ‘cognitive linguistic’ school of thought suggests that there is a single processing mechanism for language and cognition (Croft & Cruse, 2004), while a less deterministic ‘dual hierarchy’ theory suggests parallel organisation and close inter-dependency between the two domains (Perlovsky, 2015). Figure 3.12 provides a schematic representation of the dual hierarchy model. In support of the close link between language and cognition, the present findings also strongly suggest that the relationship between them does not change with age. Indeed, when controlling for age at the time of assessment, the relationship between language and non-verbal IQ remained stable and statistically significant. If one accepts a single mechanism for language and cognition, or at least close inter-dependence between the two, the necessary implication would be that proficient language skills are not possible in the absence of, and can be predicted by, non-verbal cognitive abilities, and vice versa. Although the sample size in the present study was reasonably small and thus did not allow for this hypothesis to be tested, this is an interesting avenue for future investigation in larger scale studies. Dissociations between language and cognitive skills would need to be demonstrated to challenge a single mechanism account of language and cognitive development.

3.4.4 Profound deficits in manual dexterity skills

Poor coordination and motor control are commonly occurring long-term deficits in all brain tumour survivors. One of the interim reports from the Childhood Cancer Survivor study, based on a sample of 1607 patients with any type of brain tumour, suggests figures as high as 49% for coordination
and 26% for motor control difficulties (Packer et al., 2003). With the cerebellum playing a key role in the modulation of movement, these percentages may be even higher in PFT survivors than patients with tumours affecting other brain areas. Motor deficits post cerebellar tumour are well-documented (e.g. Puget et al., 2009; Rueckriegel, Blankenburg, Henze, Baqué, & Driever, 2009; Droit-Volet et al., 2013). The present findings confirm those reported in the literature; patients demonstrated highly diminished performance in the visuo-motor control of their dominant and non-dominant hands separately, and the simultaneous use of both hands. Moreover, the discriminant function analysis revealed that performance on the Assembly test accounted for the highest proportion of the between-group differences, compared to the measures of language functioning and non-verbal intelligence. This was not surprising,
considering the functional anatomy of the cerebellum and its involvement in the modulation of motor control (Stoodley, & Schmahmann, 2010; Koziol et al., 2014). However, unlike previous studies, we were able to quantify the magnitude of the contribution of the manual dexterity deficits to the patients’ diminished multi-domain performance.

Additionally, correlational analyses revealed a moderate to high degree of association between performance on the Purdue Pegboard Assembly task and all of the scaled CELF-5 language tests, as well as performance on the non-verbal intelligence test. In other words, performance on linguistic and cognitively demanding tasks where no overt motor control was required was better in those participants who exhibited better motor regulation abilities than those who had difficulties with motor regulation. This is not entirely surprising, considering the close spatial position of the cerebello-cerebral circuitry subserving movement and cognition (Stoodley & Schmahmann, 2010). In line with the above, studies have reported a link between diminished language and cognition with poor motor control in both typically developing and clinical groups (Pexman & Wellsby, 2016). Crucially, our results, for the first time, demonstrate that manual dexterity level of performance correlates highly with all sub-components of language, assessed in the CELF-5 battery (Table 3.6), and not just the aspects of language function that rely on motor control (e.g. articulation or speech).

An understanding of the link between motor and linguistic/cognitive abilities is useful not only for the purpose
of prognostic evaluation, but also for rehabilitation practices. If there is a strong link between motor, cognitive, and linguistic functioning, it is plausible that repeated practice of skills in one area may have indirect benefits for other functional domains. This could be particularly relevant to patients with temporary post-operative mutism who are restricted in their ability to engage in verbal communication, yet are able to perform manual dexterity tasks.

3.4.5 Limitations of the study

When interpreting the results of this observational study, it is important to take into account its limitations. Firstly, the baseline of the patients’ abilities in terms of language, cognition, and manual dexterity remains unknown, as it was not assessed prior to surgery. Currently in the UK there is no formal requirement to conduct a functional assessment in paediatric PFT patients, unless they are formally entered into a research study. Although lengthy neuropsychological assessment may not be possible, basic screening would be beneficial, as it would give the families of patients a better idea as to the degree of impairment attributed to the surgery and subsequent treatment. In addition, it would provide extremely useful baseline data, should the patients be entered into research studies after the treatment has taken place.

A further important consideration is the validity of the neuropsychological assessment measures. In the present study, an American test battery (CELF-5) was used, as it provided normative data for the young adults, suitable for the purpose of the current study, and no suitable equivalent battery from the UK was available. There are, however, notable differences in American English and British English,
which may have influenced the participants’ performance, in particular on the tests assessing language comprehension (Wiig et al., 2013). For example, an American expression 'track meet' is not commonly used in Britain and is usually substituted by 'athletics contest' or similar. Every attempt was made to eliminate the effect of these differences by substituting ambiguous or unclear words for commonly used British English equivalents. Ideally, a battery validated in the country where the research takes place should be used. However, the impact of this should have been similar for both the patients and the healthy controls, so this factor was unlikely to influence the between-group comparisons.

A further limitation of the CELF-5 is that, despite being a very comprehensive language assessment test, it does not examine metalinguistic awareness. This domain is separate from the core language skills (e.g. semantics, morphology, syntax and pragmatics), and describes aspects of communication competence, such as using figurative language, understanding humour and multiple/ambiguous meanings. It is possible for a young person to acquire age-appropriate core language skills, yet lack metalinguistic awareness skills (Zipke, 2007). The initial study protocol included the CELF-5 Metalinguistics assessment battery but this was later dropped in view of the already lengthy assessment procedure. In further studies, however, metalinguistic skills should be assessed for a more thorough evaluation of communication and linguistic maturation in PFT survivors.

The choice of the control group is also an important issue to consider. In the present study, the control participants had no history of oncological or neurological disease, or in fact any other serious diagnosis that may have impacted normal
participation in educational and social activities. As a result, the healthy volunteers may have received more years of formal education compared to the study patients, who are likely to have spent a significant amount of time in treatment and recovery, isolated from their normal social surroundings. Thus, at least some of the observed differences in linguistic and intellectual functioning could have been due to a reduced duration of formal schooling and socialising in the patient group compared to the group of controls, rather than being due to the effects of the tumour and treatment alone. The present study’s protocol did not include an evaluation of the duration and intensity of schooling, which could be considered a methodological limitation. In future research, the duration of schooling should be controlled for in order to improve the internal validity of the results. However, this may also raise challenges in terms of recruiting a control group with a sufficient amount variability in schooling to make the observed correlations reliable.

An alternative strategy would be to recruit a control group from a clinical population of patients with other types of oncological disease, who have received treatment of a similar intensity and duration. In this way, matching could be achieved in relation to patients’ history of formal education and degree of participation in normal social activities. This type of comparison, however, would address a different aim to the one pursued in the present study. A clinical control group would enable isolation of the deficits specific to a given disorder (e.g. brain tumour versus leukemia). In the current study, the objective was to quantify the deviations from the optimal developmental course, that it, free from disease. For this reason, a healthy peers control group was deemed most
appropriate.

Finally, although language, non-verbal intelligence, and manual dexterity are important aspects of development, they constitute only a fraction of overall patients’ functional profiles. To fully understand the severity and complexity of the long-term impact of PFTs on development, other domains should be considered, such as neurological deficits, psychosocial functioning, adaptive skills etc. In addition, broadening the age range of participants would allow for an exploration of the relationship between the cognitive, linguistic and manual dexterity domains across development. In our study all of the participants were at least 16 years old at the time of assessment, meaning that a large amount of developmental change had already taken place and our findings may not reflect outcomes observable in early childhood.

3.4.6 Conclusions

In summary, two key conclusions can be drawn from the present investigation. First of all, the PFT patients exhibited significant deficits in terms of language, non-verbal intelligence and manual dexterity. Language deficits were observed in every domain except the single verbal memory test. Semantic processing of language was one of the functional domains where the difference between the patients and controls was most pronounced, superseded only by manual dexterity deficits. This suggests that PFT patients may be at even greater risk of developing language processing difficulties than cognitive deficits. There was less uniformity in the patients’ language performance, compared to the healthy controls, indicating that not all specific linguistic functions are affected to a similar degree. This suggests that patients can
still retain strengths in specific language functions that can potentially be built upon during rehabilitation.

Secondly, there was a strong positive relationship between language, non-verbal intelligence, and manual dexterity skills, suggesting that these domains are affected in a similar manner by the disease. Qualitatively, the relationship between the performance in all three domains was consistent amongst the patients and controls, suggesting that PFT and its treatment stunts the developmental course, rather than altering its trajectory. More specifically, the cognition/language relationship remained strong even after accounting for the effects of age. This close connection between the three functional domains may also have implications for rehabilitation; practicing skills in one area (either motor coordination, language, or nonverbal cognition) may prove beneficial for the development of skills in other functional domains.

The present study highlights the need to consider delayed language development as a frequent and significant deficit in childhood PFT survivors, alongside the well-researched deficits in general cognition and motor control. Considering the importance of language for education and social functioning, the risk of language impairment should be highlighted to the families of patients and considered as a priority area for rehabilitation.
Chapter 4: Alterations in cortical activation patterns during language tasks involving covert articulation and semantic retrieval in PFT survivors: an fMRI study

Key findings

- Patients lack metabolic response in the pre-central and post-central gyri during semantic retrieval;
- Key regions of the perisylvian language network (Broca’s, Wernicke’s and Geschwind’s areas) respond bilaterally and comparably in both groups;
- The behavioural measure of semantic access predicts a response in the left hemisphere, on the border of the lateral occipital cortex and angular gyrus;
- The behavioural measure of expressive language predicts a response in the right hemisphere: frontal pole, paracingulate gyrus, superior frontal gyrus, and middle frontal gyrus;
- Articulation of speech is associated with activation in the Crus I and Crus II of the right cerebellar hemisphere;
- Semantic retrieval is associated with activation in the Crus VI and VIIb of the vermis, as well as right lobules V and VI.

4.1 Introduction

For over a hundred years, the neurobiological underpinnings of language processing have been understood through the classical Wernicke-Lichtheim model (Poeppel et al, 2012), based on early lesion studies by Broca (1861), Wernicke (1874) and Lichtheim (1885). Geschwind’s (1979) summary,
grounded in these findings, heavily influenced modern discourse about language processing and research methodologies in this field. Subsequently, the canonical model of language processing became known as the Broca-Wernicke-Lichtheim-Geschwind model, with a set of regions surrounding Sylvain fissure in the left hemisphere thought to be facilitating language processing (Ben Shalom & Poeppel, 2008). Three key areas, located in the left hemisphere, are typically associated with this model. The Inferior Frontal Gyrus (Broca’s area), spanning Brodmann’s cytoarchitectonic (BA) areas 44-45, is referred to as the speech production centre. The Superior Temporal Gyrus (Wernicke’s area), BA22, is thought to be involved in the comprehension of written and spoken language. Finally, the Inferior Parietal Lobule (Geschwind’s area), BA 40, is where, according to the model, convergence of the multimodal sensory inputs takes place to allow the processing of semantic content (Catani & Jones, 2005).

Since the discovery of the blood-oxygenation-level dependent magnetic resonance contrast by Seiji Ogawa (1990) and a novel non-invasive technique of functional magnetic resonance imaging (fMRI), there has been an explosion of studies investigating the neural basis of the various sub-components of language. These studies span both healthy and clinical populations, and have greatly enriched the current understanding of the dynamics of language processing, expanding the canonical model. Over the years, multiple reviews and meta-analyses have attempted to summarise the findings from the fMRI studies of language (e.g., Cabeza & Nyber, 2000; Turkeltaub, Eden, Jones, & Zeffiro, 2002; Price, 2012; Weiss-Croft & Baldeweg, 2015), but the field is now
arguably too vast and increasingly sub-specialised to be covered in a single review.

A neuropsychological investigation, described in Chapter 3 of the present thesis, demonstrated language performance deficits in long-term PFT survivors. Beyond behavioural performance, it is important to investigate neurobiological factors that drive changes in overt behaviour, and fMRI offers a unique opportunity to do so non-invasively. So far, this technique has been under-utilised in research involving the PFT population. Only a handful of studies have utilised fMRI to examine aspects of working memory (Wolf et al., 2013), the benefits of prophylactic reading (Zou et al., 2016) and cognitive training (Kesler, Lacayo, & Jo, 2011). In light of the inconsistent evidence regarding language-related outcomes in PFT survivors, fMRI can add a new dimension and possibly even resolution to this debate.

4.1.1 fMRI method

Functional MRI is a technique used for studying haemodynamic changes in the brain associated with enhanced neural activity (Logothetis, 2008). It is extensively used for studying the functional neuroanatomy of motor control, cognition, language, vision, somato-sensations and emotions. fMRI utilises the differences in the magnetic properties of oxygenated and deoxygenated blood, the so-called Blood Oxygenation Level Dependency (BOLD) effect (Ogawa et al., 1990). During task performance, a network of brain regions is mobilised, triggering synaptic activity, which, in turn, is coupled through the astrocytes to vascular responses (Ogawa et al, 2012). An additional supply of blood is delivered to the active regions, with haemoglobin molecules in the red blood cells carrying oxygen. In the capillary beds, the oxygen is
extracted to the brain tissue and diamagnetic oxyhaemoglobin is converted into paramagnetic deoxyhaemoglobin. Since more blood is originally supplied than is needed, the concentration of the deoxyhaemoglobin in a given region decreases during the active state, and increases during the resting state (Cabeza and Nyberg, 2000). These differences in the magnetic properties are taken advantage of during the magnetic resonance imaging of the brain over a period of time while the person being imaged performs a cognitive task (Figure 4.1).

![Figure 4.1. The haemodynamic response and fMRI BOLD signal. From (Arthurs & Boniface, 2002)](image)

The haemodynamic response following the external stimulus is much slower than the neuronal activity; it is detectable only 4-6 seconds following the onset of the task. However, since the haemodynamic lag is relatively constant, the timing of the stimulus and haemodynamic response in relation to each other can be measured with a good level of accuracy (Menon and Kim, 1999). A model of the haemodynamic response function is shown in Figure 4.2.

The increasingly widespread application of fMRI in research has largely been facilitated by the development of rapid image acquisition techniques, notably echo-planar imaging, developed by Peter Mansfield in the 1970s and 1980s (Huettel et al., 2004).
4.1.2 Studying language function with fMRI in healthy and clinical populations

Investigations into the neural basis of language processing experienced an unprecedented boom after the development of the fMRI technique, which quickly became more popular compared to the previous imaging method of choice, Positron Emission Tomography (PET). The first fMRI studies of language were published not long after the BOLD effect was described (e.g., McCarthy, Blamire, Rothman, Gruetter, & Shulman, 1993; Hinke et al., 1993). Initially focusing on the feasibility of the method itself, language fMRI research gradually branched out to include the study of a multitude of language processing components.

Price (2012) carried out a comprehensive review of the PET and fMRI language studies in the first 20 years of fMRI application, offering a summative map of the cortical areas implicated in different aspects of language processing (Figure 4.3). The map demonstrates just how much has been learnt about the cortical modulation of language processing since the classical Broca-Wernicke-Geschwind model emerged. In
addition to the inferior frontal gyrus (Broca’s areas), the superior temporal gyrus (Wernicke’s area) and Inferior Parietal Lobule (Geschwind’s area), activation during the performance of various language-related tasks was observed within the cerebellum, anterior cingulate, basal ganglia and occipital cortex. The increasing availability of fMRI has arguably facilitated the shift from the modular understanding of language, based on the classical Broca-Wernicke-Geschwind’s model, to recognition of its dynamic nature and network-like properties (Blumstein & Amso, 2013).

Beyond studying language with the use of fMRI in the healthy population, this method provides a unique opportunity for investigating the relationship between language impairments and illness- or injury-related lesions. In the 19th century, when Paul Broca first reported the landmark case of the patient Leborgne, whose speech production was restricted to a single word ‘tan’, he could only describe an associated lesion in the left inferior frontal lobe after the autopsy. Nowadays, fMRI enables the examination of both lesioned and spared brain regions’ functioning in-vivo. As one of many examples, numerous fMRI studies have confirmed Broca’s conclusion about the involvement of the described area (which was subsequently named after him) in the production of speech (Huettel et al., 2004). Moreover, fMRI study of lesioned brains has shed light on brain plasticity and the re-organisation of the functional architecture related to language processing following injury (e.g., Staudt et al., 2002; Liegeois, Connelly, Baldeweg, & Vargha-Khadem, 2008). Finally, pre-operative fMRI is proving to be a useful neurological tool for mapping of the language-implicated areas with the purpose of sparing
Figure 4.3. Summative map of the areas where cortical activations were reported during various language processing tasks in fMRI studies between 1992 and 2012. From (Price, 2012).

as many functions as possible after the removal of brain tumours (Guissani et al., 2010).

4.1.3 Challenges associated with imaging the cerebellum

fMRI has become an invaluable tool for exploring the involvement of the cerebellum in language and cognition. Although the association between cerebellar damage and
speech disturbances has been known about since the early 20th century (Holmes, 1917), the investigation of subtler linguistic deficits was limited to behavioural methods.

Compared to the cerebral cortex, there are additional methodological challenges associated with functional imaging of the cerebellum, which are discussed in detail by Schleft, Weistler, Verstynen, & Diedrichsen (2014). Notably, the small size of the cerebellar structures (each lobule is between 5 and 10 mm) means that the signal is being averaged across closely positioned structures, yet those structures have different functional specialisation and connectivity (Stoodley & Schmahmann, 2009). In addition, inter-individual normalisation of cerebellar images has proven to be challenging, especially in respect to the deep cerebellar nuclei, positioned within the cerebellar white matter. The dentate nucleus is a particularly important structure, implicated in cognitive processing, but the BOLD signal obtained from it is lower than that of the surrounding white matter or cerebellar cortex (Dimitrova et al., 2006). Finally, the dense vascular bed surrounding the cerebellum and brainstem provide an additional source of physiological artefacts in fMRI images, such as heartbeat and respiration. All of these challenges are gradually being addressed with the development of more detailed cerebellar atlases for fMRI normalisation (Diedrichsen, Balster, Flavell, Cussans, & Ramani, 2009; Diedrichsen et al., 2011), using higher magnetic field strength (e.g., Kuper et al., 2011, Thurling et al., 2012) and recording physiological parameters in order to isolate the noise from the task-evoked signal (Schleft et al., 2014).
Chapter 4

4.1.4 Aims and hypotheses

The present study set out to investigate aspects of language processing in PFT survivors, using task-based fMRI. To date, the linguistic abilities among this group of patients have been investigated using only behavioural methods, with the exception of a single recent study, which examined the effects of reading intervention on the cortical activation patterns in medulloblastoma survivors (Zou et al., 2016). Thus, the present study is novel in many ways and pursues several aims:

- to map BOLD signal fluctuations during the articulation of words with and without semantic load in long-term survivors of PFTs, and compare the patterns obtained to those of healthy peers;
- to probe and quantify changes in signal intensity within the bilateral regions of interest, comprising the canonical supratentorial language network (Broca’s, Wernicke’s and Geschwind’s areas);
- to examine the predictive value of the overt language performance scores on signal changes within the supratentorial areas, and whether these changes are modulated by non-verbal intelligence in both PFT survivors and healthy controls;
- to examine the cerebellar cortical BOLD activity in healthy volunteers with an intact posterior fossa in order to extend the knowledge of the cerebellar involvement in the processing of the language tasks utilised in the current study.

We hypothesised that there would be observable differences in the patterns of supra-tentorial activation between the PFT
survivors and the healthy controls. Due to the lack of literature in this area, it is difficult to theorise about specific features of this difference, so a data-driven approach to the interpretation of the results has been adopted. We expected to see that Broca’s area would be implicated in speech articulation when semantic load was both present and absent. On the contrary, Wernicke’s and Geschwind’s areas would be engaged only when semantic load was included in the task, and there would be observable differences in the ways in which these three areas were engaged between the patients and healthy controls.

We also expected that the observed cerebellar activation in a healthy control group would be in accordance with the current understanding of the cerebellar functional architecture, that is, the right cerebellum would be preferentially engaged in the semantic processing, while the medial/vermal areas would be engaged in motoric speech articulatory planning.

4.2 Method

4.2.1 Functional MRI protocol

All of the neuroimaging was performed at the Sir Peter Mansfield Magnetic Resonance Centre on a 3T Philips scanner using a 32-channel head coil. The imaging protocol consisted of a T1-weighted MPRAGE structural scan (TR = 8.1 ms, TE = 3.7 ms, TI = 960 ms, FOV - 25.6 X 25.6 mm$^2$, 256x256 matrix, voxel size 1x1x1 mm, 160 slices,), 3 X functional MRI scans (T2*-weighted single-shot gradient echo pulse sequence (EPI): TR = 2500 ms, TE = 35 ms, flip angle = 75°. Matrix size = 64 x 64 x 40, voxel size 3x3x3 mm) and a Diffusion Weighted Scan (TR = 12000 ms, TE = 54.52 ms, $b$ = 1000, voxel size 2x2x2 mm, 32 diffusion directions).
4.2.2 Participants

Participants were recruited from the same cohort of subjects described in Chapter 3. 16 patients and 20 healthy controls were scanned. Details of the patients can be found in Table 4.1.

4.2.3 Procedure

fMRI was performed as part of the general MRI assessment, during the second research visit, typically several weeks after the neuropsychological assessment had taken place. The visit schedule is presented in Table 4.2.

All participants were trained to perform the fMRI tasks outside of the scanner. The training lasted for as long as necessary to ensure that each participant knew exactly how to perform the tasks. Female participants were also offered a pregnancy test as pregnancy was one of the study exclusion criteria. Once inside the MRI scanner, the participants lay flat on their backs and were asked to keep as still as possible. Ear plugs and ear defenders were provided for protection from scanner noise. Foam pads were placed either side of the subject’s head to restrict head movement. A screen was positioned in front of the scanner and the head mirror was adjusted in order for the participants to see the images presented on the screen. Participants were also given an MRI compatible button box, which they held in the dominant hand. A button press was required throughout the task in response to the randomly appearing red square, as a measure of attentional control.
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<th>Recovery Time*</th>
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<td>95</td>
</tr>
<tr>
<td>E4</td>
<td>F</td>
<td>16:0</td>
<td>20:11</td>
<td>4:11</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>No</td>
<td>102</td>
<td>95</td>
<td>120</td>
</tr>
<tr>
<td>C3</td>
<td>F</td>
<td>16:10</td>
<td>21:9</td>
<td>4:11</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>No</td>
<td>86</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>L6</td>
<td>F</td>
<td>16:7</td>
<td>18:10</td>
<td>2:3</td>
<td>AC</td>
<td>ML</td>
<td>No</td>
<td>Yes</td>
<td>R</td>
<td>No</td>
<td>59</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>C7</td>
<td>M</td>
<td>11:6</td>
<td>17:8</td>
<td>6:2</td>
<td>MB</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>No</td>
<td>108</td>
<td>104</td>
<td>110</td>
</tr>
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<td>J7</td>
<td>M</td>
<td>1:0</td>
<td>17:3</td>
<td>16:3</td>
<td>MB</td>
<td>ML</td>
<td>No</td>
<td>Yes</td>
<td>R</td>
<td>No</td>
<td>92</td>
<td>98</td>
<td>90</td>
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<tr>
<td>S7</td>
<td>F</td>
<td>12:9</td>
<td>17:11</td>
<td>5:2</td>
<td>MB</td>
<td>4thV</td>
<td>Yes</td>
<td>Yes</td>
<td>L</td>
<td>Yes</td>
<td>90</td>
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<td>17:6</td>
<td>12:5</td>
<td>AC</td>
<td>ML</td>
<td>No</td>
<td>No</td>
<td>L</td>
<td>No</td>
<td>88</td>
<td>93</td>
<td>80</td>
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<tr>
<td>M78</td>
<td>F</td>
<td>8:0</td>
<td>17:3</td>
<td>9:3</td>
<td>E</td>
<td>4thV</td>
<td>Yes</td>
<td>No</td>
<td>R</td>
<td>No</td>
<td>88</td>
<td>83</td>
<td>80</td>
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<tr>
<td>E58</td>
<td>F</td>
<td>8:0</td>
<td>17:4</td>
<td>9:4</td>
<td>AC</td>
<td>BS</td>
<td>Yes</td>
<td>No</td>
<td>L</td>
<td>No</td>
<td>84</td>
<td>89</td>
<td>80</td>
</tr>
<tr>
<td>C9</td>
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<td>11:6</td>
<td>16:7</td>
<td>5:1</td>
<td>AC</td>
<td>RC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>No</td>
<td>96</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>I9</td>
<td>F</td>
<td>7:9</td>
<td>16:8</td>
<td>8:11</td>
<td>AC</td>
<td>RC</td>
<td>No</td>
<td>No</td>
<td>R</td>
<td>No</td>
<td>78</td>
<td>85</td>
<td>55</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>10:1</td>
<td>17:9</td>
<td>7:8 (3:8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>87.69</td>
<td>91.81</td>
<td>86.88</td>
</tr>
</tbody>
</table>

Once the participant was comfortable and ready to begin, the scanning process commenced. The fMRI was performed following the T1-structural scan. There were three fMRI runs for most of the participants, each lasting between five and six minutes. One patient and one healthy volunteer completed two fMRI runs each, due to a late appointment start and timing restrictions.

**4.2.4 Functional MRI task**

**4.2.4.1 Paradigm selection**

There are several widely used methods of designing fMRI tasks, including a subtraction paradigm, a factorial design, a parametric design and a conjunction analysis. All of them assume linearity between the condition presentation and BOLD response, and differ in regard to the choice of baseline, the ability to test the interaction between the individual conditions within the task and the response to a task of gradually increasing difficulty (see Amaro & Barker (2006) for a detailed overview of the commonly used paradigms).

The fMRI paradigm in the present study was designed in accordance with the principle of the conjunction design. It assumes that two or more conditions in the paradigm can share a cognitive component of interest. This permits analysis of the processes involved in the performance of each component separately, as well as the entire run when they are combined. Figure 4.4 represents the schematic diagram of the application of the conjunction principle to the fMRI task in the current study, informed by the paradigms successfully used in the fMRI language studies published by other authors. The semantic retrieval (SR) condition, whereby participants generate words in response to visual stimuli, requires both
### Table 4.2
**Neuroimaging assessment: Visit 2 schedule**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Purpose</th>
<th>Time required</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMRI safety questionnaire</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>fMRI task practice</td>
<td>To ensure full understanding and ability to perform the fMRI task</td>
<td>20-30 minutes</td>
</tr>
<tr>
<td>Break/ Setting up participant in the scanner</td>
<td></td>
<td>15 minutes</td>
</tr>
<tr>
<td>Localiser scan</td>
<td>To determine the location of the subject’s head in the three scanner-frame axes</td>
<td>5 minutes</td>
</tr>
<tr>
<td>T1-weighted structural scan</td>
<td>To provide anatomical reference for the MRI data analysis</td>
<td>6-7 minutes</td>
</tr>
<tr>
<td>fMRI run 1</td>
<td>To obtain a BOLD contrast map of neural response during the fMRI task performance</td>
<td>5-6 minutes</td>
</tr>
<tr>
<td>fMRI run 2</td>
<td>As above</td>
<td>5-6 minutes</td>
</tr>
<tr>
<td>fMRI run 3</td>
<td>As above</td>
<td>5-6 minutes</td>
</tr>
<tr>
<td>DWI scan</td>
<td>To obtain a diffusion map of the brain</td>
<td>6-7 minutes</td>
</tr>
<tr>
<td>Total scanning time</td>
<td></td>
<td>47 minutes</td>
</tr>
<tr>
<td>Total visit time</td>
<td></td>
<td>1 hour 10 minutes - 1 hour 30 minutes</td>
</tr>
</tbody>
</table>

speech articulation and access to the meaning of the images and associated words (Thompson-Schill et al., 1998; Frings et al., 2006). Articulation of speech (AS), however, is a more basic task where participants are simply required to repeat highly rehearsed words on the loop with minimal semantic processing (Wildgruber, Ackermann, Klose, Kardatzki, & Grodd, 1996; Ackermann, Wildgruber, Daum, & Grodd, 1998). By adding or removing the semantic component to the basic word repetition task, it is possible to segregate the BOLD
response associated with the mechanical articulation of speech from the one associated with semantic processing.

4.2.4.2 Task design

Task-based fMRI studies typically employ either a blocked design, an event-related design or a combination of the two. In a blocked design, the duration and order of the conditions are pre-set by the researcher. It is assumed that an independent variable is kept constant throughout the block. The advantage of this design is greater control over the task administration and manipulation of the independent variable. Blocked designs are generally considered to be more powerful for detecting significant fMRI activity, but less powerful when it comes to estimating the time course of the evoked activity (Amaro & Barker, 2006). The opposite is true for an event-related design, where the order of the conditions is randomised; the observed activity can be time-locked to the signal onset with better precision, but the detection power may be significantly reduced, especially if the duration of the event is too short for the associated haemodynamic response to take place (Huettel, Song, & McCarthy, 2004).

The fMRI task design in the current study combined features of the blocked and event-related designs in order to maximise each method’s benefits and minimise the disadvantages. The onset and duration of the conditions were randomised. However, for the Semantic Retrieval and Covert Articulation conditions, a minimum duration of nine seconds was set in order to ensure sufficient time for the BOLD response to take place. Control null-task blocks (a white gaze-fixation dot in the centre of a blank grey screen) were included as a baseline
Figure 4.4. Application of the conjunction principle to the fMRI task design in the present study: schematic representation. Covert articulation is a common component for both CA and SR conditions.

state. A randomly-presented red screen was included in the task as a way of further ensuring attentional control; participants were instructed to press the button on the handheld button box whenever they saw the red screen appear. The overall duration of a single fMRI run was limited to under 6 minutes in order to reduce the effects of fatigue, and three runs were repeated per participant.

The task was designed and presented using the PsychoPy2 v1.81.03 software (Peirce, 2007; Peirce, 2009). A schematic diagram of the task is available in Figure 4.5. In the first condition (Semantic Retrieval), participants were shown images of nature scenes and asked to subvocally generate the name of the season they could associate with that image (‘spring’, ‘summer’, ‘autumn’ or ‘winter’). Each image was presented on the screen for three seconds. In the second
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condition (Covert Articulation), participants were instructed to subvocally recite names of the seasons at a normal conversation pace without breaks (e.g. ‘spring-summer-autumn-winter-spring-...’). Using the same range of words enabled control of the lexical output. Control of the visual input was achieved by using a phase-scrambled version of the seasonal images from the first condition. The colour was removed from both the original and scrambled images in order to minimise the possibility of semantic processing of the scrambled images. For example, an autumn image may predominantly contain shades of red, which would still remain after the phase-scrambling, triggering an unwanted association of the scrambled image with this particular season. Figure 4.6 shows examples of the stimuli; the full set of experimental stimuli and the task script are available in Appendices 6 and 7.

Figure 4.5. Example of a single fMRI run timing. R - Rest, CA - Covert Articulation, SR - Semantic Retrieval, A - Attention control button press. The condition order and duration were randomised for each run and each participant. Each condition lasted for a minimum of 9 seconds to enable the BOLD response to take place. The overall run duration was between 300 and 360 seconds

4.2.5 Imaging data pre-processing

The fMRI and T1-weighted anatomical scan data were received from the scanner in DICOM (Digital Imaging and Communications in Medicine) format and transformed into NIFTI (Neuroimaging Informatics Technology Initiative) format, which is suitable for analysis using the FSL
Figure 4.6. Examples of the fMRI stimuli: A. Semantic Retrieval condition, B. Covert Articulation condition, C. Null-task condition (rest), D. Attention control condition: participants were required to press the button as soon as the red screen appeared. During the task, participants were asked to focus on the centre of the screen, marked with the white dot.

Software (Smith et al., 2004, Jenkinson et al., 2012) available www.fmrib.ox.ac.uk/fsl. Prior to the analysis, 4D fMRI images were visually inspected for quality and any obvious artefacts using the FSLView tool (Flitney et al., 2007). Non-brain tissues were removed from the high-resolution T1-weighted images and fMRI images using the FSL BET tool (Smith, 2012).

The fMRI time-series data obtained were subjected to the standard pre-processing steps in order to reduce the variability in the data, not associated with the task:

- motion correction - to reduce the effect of head motion
during the experiment, using the FSL MCFLIRT tool (Jenkinson, Bannister, Brady & Smith, 2002). This tool uses a rigid body transformation method with the middle image in the time-series used as a template;
- temporal filtering - to remove low frequency artefacts. The high pass filter cutoff was set to 90 seconds;
- spatial smoothing - to increase the signal power by replacing the individual voxel signal with the weighted average of the surrounding area. The full-width at half-maximum level for spatial smoothing was set to 5 mm (default in FSL);
- spatial normalisation - to register individual images to standard space in order to allow comparisons among different brains. MNI T1 2 mm-voxel standard space, available in the FSL file library, was used as a reference image.

4.2.6 Regions of interest

The regions of interest (ROIs) were located based on the description of the perisylvian language network, which is currently widely accepted as a set of supra-tentorial regions underpinning language processing (Catani & Jones, 2005; Catani & Mesulam, 2008; Xiang, Fonteijn, Norris, & Hagoort, 2010; Price, 2012). Six spherical regions of interest, each 5 mm in diameter, were manually created in the MNI space; Left Broca’s area (L-BA), Right Broca’s area (R-BA), Left Wernicke’s area (L-WA), Right Wernicke’s area (R-WA), Left Geschwind’s area (L-GA) and Right Geschwind’s area (R-GA). L-BA and and R-BA were centred in the vicinity of the Inferior Frontal Gyrus (IFG), BA 44; L-WA and R-WA in the Superior Temporal Gyrus (STG), BA 22; L-GA and R-GA in the Inferior
Parietal Lobule (IPL), BA 40. The ROIs and associated coordinates in the MNI space are presented in Figures 4.7, 4.8 and 4.9.

4.2.7 Data analyses

For all levels of the analysis, registration to high resolution structural and/or standard space images was carried out using the FSL FLIRT tool (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). For both the structural and standard space registration, a full linear search with 12 degrees of freedom was applied, as this, on visual inspection, resulted in the best level of registration. The Z statistic images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$ (Worsley, 2001).

Figure 4.7. Broca’s area spherical ROI masks (5 mm diameter). A: Left Broca’s area, MNI coordinates $x = -52$, $y = 20$, $z = 6$, B: Right Broca’s area, MNI coordinates $x = 52$, $y = 20$, $z = 6$
Figure 4.8. Wernicke’s area spherical ROI masks (5 mm diameter). A: Left Wernicke’s area, MNI coordinates x=-54, y=-32, z=4, B: Right Wernicke’s area, MNI coordinates x=54, y=-32, z=4

Figure 4.9. Geschwind’s area spherical ROI masks (5 mm diameter). A: Left Geschwind’s area, MNI coordinates x=-54, y=-26, z=26, B: Right Geschwind’s area, MNI coordinates x=54, y=-26, z=26
4.2.7.1 fMRI: first level analysis (single run)

The purpose of the first-level analysis was to extract cortical activation maps for each participant in a single task run. The analysis was set up using the FSL FEAT graphic user interface. As the timing of the condition onset had been randomised for each participant and each run, this process could not be automated and had to be carried out separately for each run one by one. Three explanatory variables (EVs) were specified: Semantic Retrieval, Covert Articulation and Attention-control button press. A number of contrasts were specified to investigate the activation associated with each condition. The most informative contrasts are discussed in the Results section.

The basic shape of the waveform describing the modelled stimuli was set to the Custom 3-column format, which allowed the finest level of control over the input waveform. This required specification of the exact timing for the condition onset and duration. The timings were extracted from the PsychoPy output files and converted into text files, readable by FSL software. Three timing files were constructed for each run: Semantic Retrieval, Covert Articulation and attention-control button press. The null-task (rest) timings were inferred by deducting all of the mentioned tasks from the total fMRI run. The Double-Gamma HRF convolution method was used as it combines the benefit of a standard positive function with a normal lag, and a small inverted gamma that models post-stimulus undershoot. Appendix 9 provides an example of a typical timing file and a design matrix in the first-level analysis.
4.2.7.2 fMRI: second level analysis (within-subject)

The aim of this stage of the analysis was to estimate each subject’s mean response using a paired t-test. Each first level analysis contained six contrasts; thus, there were six COPE (Contrast of Parameter Estimates) outputs in each first-level .feat directory. The second-level analysis was carried out independently on each of these contrasts (six second-level analyses in total). For each analysis the design matrix was the same and contained 106 input .feat files (one for each fMRI run) and 36 contrasts (one for each participant), see Appendix 10.

Fixed effects (FE) higher level modeling was applied because, firstly, it is more sensitive to activation, and secondly, the objective at this stage was to infer within-subject rather than population effects, for which mixed-effects (ME) modelling is more appropriate (Beckmann, Jenkinson, & Smith, 2003). As an outcome of this stage of the analysis, a single .gfeat directory was created, containing six COPE directories, one for each contrast from the first-level analysis. Each COPE directory contained 36 activation maps, one for each participant for that particular contrast.

4.2.7.3 fMRI: third level analysis (between-subject)

At this stage of the analysis, the aim was to use subject means from the second-level analysis in order to model the between-subject variance and estimate the mean difference in response between the patients and healthy volunteers, using an unpaired t-test. Because it was assumed that the observed differences would allow for making population-wide
inferences, mixed-effects (ME) modelling was used (Beckmann, Jenkinson, & Smith, 2003).

Six third-level analyses were performed, one for each COPE from the second-level analysis output. For each analysis, the design matrix was the same and contained 36 cope.feat input files (one for each participant) and four contrasts (one for each type of mean difference estimated: patients>controls, controls>patients, patients’ mean response and controls’ mean response). The design matrix is available in Appendix 11.

4.2.7.4 Regression analyses: whole-brain voxel-wise approach, using CELF-5 index scores as predictors

It was also of interest to see whether overt language performance outside of the scanner was predictive of the metabolic response inside the scanner. The predictive value of overt language performance on haemodynamic response during the fMRI task was assessed by including CELF-5 indices in the model as covariates. Two indices were selected for this purpose. The Language Content Index (LCI), as a measure of semantic access, was used for predicting the change in signal during the associated fMRI Semantic Retrieval condition. The Expressive Language Index (ELI) score, as a measure of language production, was used for predicting the change in signal during the associated fMRI Covert Articulation condition. For the purpose of the regression analyses, the patients and controls were treated as a single group. Additional contrasts were then set up to assess interaction effects, that is, whether the strength of association between the behavioural scores and the BOLD signal change differed between the patients and healthy controls.
As a result of this step of the analysis, two maps of clusters were obtained: one for the Semantic Retrieval condition, where a change in signal is predicted by the LCI, and one for the Covert Articulation condition, where signal change is predicted by ELI. The design matrix for the LCI/Semantic Retrieval regression is available in Appendix 12; the associated interaction analyses design matrix can be found in Appendix 13. The design matrix for the ELI/Covert Articulation regression is available in Appendix 14; the associated interaction analyses design matrix can be found in Appendix 15.

In the subsequent step, the values of the percentage change in signal intensity were extracted from the centres of gravity (COGs) of the detected clusters for all of the participants. The main purpose of this step was to quantify the predictive strength of the language performance on the signal fluctuation in the centres of the detected clusters as these values are not readily available in the files produced by FSL. In addition, an adjustment for the effect of non-verbal IQ as a potential confounder was made in order to determine the amount of unique influence of the language indices on the signal intensity change within cluster COGs (see Appendices 16 and 17 for the design matrices of the regression analysis with the adjustment for non-verbal IQ).

4.2.7.5 Cerebellar activation analyses in a healthy control group

Separate cerebellar analyses were performed for the healthy control group only, in order to identify areas of the metabolic response during Semantic Retrieval and Covert Articulation conditions. This type of analysis was not possible in the
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patient group due to the irregular anatomy of the posterior fossa structure following surgical intervention and associated problems with image registration to a standard template. Without reliable registration, robust group statistical analyses are not possible.

The cerebellum was isolated as an ROI from the rest of the brain during the pre-threshold masking stage (Figure 4.10), in order to limit the number of familywise error corrections. One-sample t-test was applied to construct single-group average maps of activation during the Semantic Retrieval and Covert articulation (see design matrix in Appendix 18). These maps were then contrasted to isolate the voxels where activation was unique to either condition (Semantic Retrieval > Covert Articulation and Covert Articulation > Semantic Retrieval)

Figure 4.10. Mask of the cerebellum (yellow)

4.2.7.6 Region of interest (ROI) analyses

One of the study's aims was to investigate the response evoked within canonical language-associated areas during the fMRI task. Three key areas were located on the MNI atlas (Broca’s, Wernicke’s and Geschwind’s) bilaterally, and six spherical ROIs were defined (L-BA, L-WA, L-GA, R-BA, R-WA and R-GA), as described in section 4.2.6. The values of the
mean change in signal intensity during fMRI task performance were extracted from these regions of interest for all of the participants, using the Featquery tool, for further analyses (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/UserGuide#Featquery).

The data were examined for normality using a Shapiro-Wilk test in order to apply parametric statistical procedures. A three-way mixed ANOVA, with the condition (Semantic Retrieval, Covert Articulation); ROI (L-BA, L-WA, L-GA, R-BA, R-WA, R-GA) as the within-subject factor, and the group (patients, healthy controls) as the between-subject factor, was performed in order to examine the factors affecting the percentage change in signal within the specified regions during the in-scanner task performance.

The main effects of the group (patients, healthy controls), condition (Semantic Retrieval, Covert Articulation) and ROI (L-BA, L-WA, L-GA, R-BA, R-WA and R-GA) on the signal change were examined. In addition, the two-way (group*condition, group*ROI, condition*ROI) and three-way interaction effects (group*ROI*condition) on signal intensity change were analysed. Interaction effects are informative when it comes to investigating how signal changes in a given ROI change as a function of a particular condition or group membership. Where statistically significant interactions were detected, post-hoc t-tests were performed to determine the source of the observed differences.

4.2.8 Standard space and anatomical atlases

The MNI152 (Montreal Neurological Institute) is a widely used coordinate system, derived from 152 individuals’ T1-weighted structural scans that were averaged following high-
dimensional nonlinear registrations. For localisation of the activation clusters, the present study utilised several atlases, available as part of the FSL package. The Harvard-Oxford cortical and sub-cortical structural atlases are probabilistic atlases covering 48 cortical and 21 subcortical areas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007). Both of these atlases were developed based on the T1-weighted images of 37 healthy adults and affine-registered to the MNI space. The Probabilistic Cerebellar Atlas (Diedrichsen et al., 2009) was created by averaging the cerebellar lobule masks of 20 individuals and aligned to the MNI space by both affine and non-linear registration approaches. Figure 4.11 provides a schematic illustration of the brain regions covered by the three atlases.

![Figure 4.11. Schematic illustration of the atlases, used for cluster description. A. Harvard-Oxford cortical structures atlas, B. Harvard-Oxford sub-cortical structures atlas, C. Probabilistic cerebellar atlas](image)

**4.3 Results**

**4.3.1 Semantic retrieval, between-group differences in activation**

Contrasting average activation maps for the groups during the Semantic Retrieval condition revealed that in the healthy control group there was
one cluster where the activation was significantly higher compared to the patients. A cluster containing 1249 voxels (33 723 mm$^3$) was located predominantly within the right hemisphere, Post-central and Pre-central gyrus area (Table 4.3, Figure 4.12). The opposite contrast did not produce any significant clusters, meaning that the cortical activation in the patients during the Semantic Retrieval did not exceed the activation observed in the healthy controls in any location.

### Table 4.3

*Clusters of significant difference in BOLD signal during the Semantic Retrieval condition for the contrasts healthy controls > patients and patients > healthy controls*

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$ Value</th>
<th>Max Z-stat value</th>
<th>Centre of gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$x$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$y$</td>
<td>$y$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$z$</td>
<td>$z$</td>
</tr>
</tbody>
</table>

**Healthy controls > Patients**

<table>
<thead>
<tr>
<th>1</th>
<th>1249</th>
<th>$1.55E-05$</th>
<th>3.85</th>
<th>38</th>
<th>$28%$ Right Postcentral Gyrus, $8%$ Right Precentral Gyrus, $1%$ Right Supramarginal Gyrus, anterior division</th>
<th>10.1</th>
<th>$8%$ Right Precentral Gyrus, $3%$ Right Juxtapositional Lobule Cortex (Supplementary Motor Cortex)</th>
</tr>
</thead>
</table>

**Patients > Healthy controls**

| - | - | - | - | - | - | - | - |
Figure 4.12. Areas of increased activation in the healthy controls, compared to the patients, during the Semantic Retrieval condition. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
4.3.2 Covert articulation, between-group differences in activation

Contrasting average activation maps for the groups during the Covert Articulation condition did not reveal any significant clusters on either Healthy controls > Patients or Patients > Healthy controls contrasts, indicating that there were no loci in either group where the activation significantly exceeded that observed in the other group.

4.3.3 Regression analyses of the predictive value of CELF-5 indices on the BOLD response

The predictive value of overt language performance on haemodynamic response during the fMRI task was assessed by including the CELF-5 indices in the regression model, described in section 4.2.7.4 and Appendices 12-17.

4.3.3.1 LCI and Semantic Retrieval

There was a significant positive relationship between the LCI scores and signal intensity change during the Semantic Retrieval task within three distinct clusters. Two of them were located within subcortical regions, occupying structures within basal ganglia and adjacent white matter. Cluster one, comprised of 982 voxels (26 514 mm$^3$), had a peak activity within the left cerebral white matter and Amygdala, and its centre of gravity was located within the Left Putamen. Cluster two contained 753 voxels (20 331 mm$^3$) and spanned the right thalamus and close-by right cerebral white matter. Cluster three (746 voxels, 20 142 mm$^3$) was located predominantly within the superior division of the left lateral occipital cortex, adjacent to the angular gyrus (Table 4.4, Figure 4.13). Interaction contrasts did not reveal any statistically significant
results, meaning that the strength of the association between the LCI and BOLD signal change during the Semantic Retrieval task was the same for both the patients and healthy controls.

Table 4.4
Clusters where a change in signal during the Semantic retrieval condition was significantly predicted by the Language Content Index CELF-5 score

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$</th>
<th>Max Z-stat value</th>
<th>Centre of gravity</th>
<th>Anatomical location (probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$y$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$z$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Positive association

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$</th>
<th>Max Z-stat value</th>
<th>Centre of gravity</th>
<th>Anatomical location (probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>982</td>
<td>.000142</td>
<td>4.34 -22</td>
<td>57% Left Cerebral White Matter, 23% Left Amygdala, 12% Left Cerebral Cortex, 5% Left Pallidum</td>
<td>82% Left Putamen, 12% Left Cerebral White Matter, 2% Left Pallidum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>753</td>
<td>.00121</td>
<td>4.07 12</td>
<td>34% Right Cerebral White Matter, 22% Right Cerebral White Matter</td>
<td>14% Right Cerebral White Matter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>746</td>
<td>.00129</td>
<td>4.3 -44</td>
<td>60% Left Lateral Occipital Cortex, superior division, 6% Left Angular Gyrus, 1% Left Lateral Occipital Cortex, inferior division</td>
<td>59% Left Lateral Occipital Cortex, superior division, 7% Left Angular Gyrus, 6% Left Lateral Occipital Cortex, inferior division</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Negative association

*Corrected for familywise error.
Coordinates in MNI space, anatomical location according to Harvard-Oxford subcortical structural atlas and Harvard-Oxford cortical structural atlas
Figure 4.13. Areas where a change in signal during the Semantic Retrieval condition was significantly predicted by the Language Content Index CELF-5 score. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
The values of the percentage change in signal intensity were extracted from the centres of gravity (COGs) of the detected clusters for all of the participants. The relationships with LCI indices were further quantified first without and then with the adjustment for non-verbal IQ (Table 4.5).

**Cluster 1**

Before the adjustment for non-verbal IQ, it was found that LCI explained 20.8% of the variation in signal within the COG of Cluster 1 ($F(1,34) = 8.93, p = .005, R^2 = .20, R^2_{\text{Adjusted}} = .19$). LCI significantly predicted a change in signal within the COG of Cluster 1 ($r = .46, t (35) = 2.99, p = .005$). Following the adjustment for non-verbal IQ, the effect of LCI was no longer significant. The model explained 20.9% of the variation in signal within the COG of Cluster 1 ($F (2, 33) = 4.36, p = .021, R^2 = .21, R^2_{\text{Adjusted}} = .16$). LCI was no longer predictive of a change in signal within the COG of Cluster 1 ($r = .43, t (35) = 2, p = .053$). The unstandardised B – coefficient reduced by more than 10% (from .007 to .006), implying that RPM was an important confounder.

**Cluster 2**

Before the adjustment for non-verbal IQ, it was found that LCI explained 10.2% of the variation in signal within the COG of Cluster 2 ($F(1,34) = 3.85, p = .06, R^2 = .10, R^2_{\text{Adjusted}} = .08$). LCI did not significantly predict a change in signal within the COG of Cluster 2 ($r = .32, t (35) = 1.96, p = .06$). Following the adjustment for non-verbal IQ, the effect of LCI remained non-significant. The model explained 14.1% of the variation in signal within the COG of Cluster 2 ($F (2, 33) = 2.70, p = .08, R^2 = .14, R^2_{\text{Adjusted}} = .09$). LCI was not predictive of a change in signal within the COG of Cluster 2 ($r = .14, t (35) = .61, p = .55$). The unstandardised B – coefficient reduced
### Table 4.5  
**Predictive value of LCI on the change in signal during the Semantic Retrieval condition in the COGs of the cluster detected by the whole-brain voxel-wise analyses, before and after the adjustment for non-verbal IQ**

<table>
<thead>
<tr>
<th>Cluster</th>
<th>EV</th>
<th>B (95% CI)</th>
<th>r</th>
<th>R²_a</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without the adjustment for non-verbal IQ</td>
<td>With the adjustment for non-verbal IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>r</td>
<td>R²_a</td>
<td>p</td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>LCI</td>
<td>.007</td>
<td>.46</td>
<td>.19</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>(.002 to .011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>LCI</td>
<td>.004</td>
<td>.32</td>
<td>.08</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>(.14e-2 to .008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LCI</td>
<td>.015</td>
<td>.60</td>
<td>.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>(.008 to .023)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPM</td>
<td>-.006</td>
<td>-.31</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(.014 to .001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cluster – refers to clusters described in Table 4.3  
EV – Explanatory variable  
B – Slope (estimated percentage increase in signal intensity per one LCI or RPM score point increase)  
95% CI – 95% confidence interval for the slope  
r - standardized residual  
R²_a – Adjusted coefficient of determination, indicating proportion in signal variance, explained by the model  
LCI – language content index  
RPM – Raven’s progressive matrices

by more than 10% (from .004 to .002), implying that RPM was an important confounder.

**Cluster 3**

Before the adjustment for non-verbal IQ, it was found that LCI explained 36% of the variation in signal within the COG of Cluster 3 (F(1,34) = 19.16, p < .001, R² = .36, R²_Adjusted = .34). Thus, LCI significantly predicted a change in signal within the COG of Cluster 3 (r = .60, t (35) = 4.38, p < .001).
Chapter 4

Following the adjustment for non-verbal IQ, the effect of LCI remained statistically significant. The model explained 41% of the variation in signal within the COG of Cluster 23 (\(F(2, 33) = 11.46, p < .001, R^2 = .41, R^2_{\text{Adjusted}} = .37\)). Thus, LCI was predictive of a change in signal within the COG of Cluster 3 (\(r = .81, t(35) = 4.14, p < .001\)) (Figure 4.14). The unstandardised B–coefficient in this case increased from .015 to .021, implying that RPM was not an important confounder.

Figure 4.14. Illustration of the significant predictive relationship between LCI and mean percentage signal change within the centre of gravity (COG) of Cluster 3 during the Semantic Retrieval condition. The present cluster was one of three identified by the whole-brain voxel-wise regression analyses, but the only one where the relationship remained significant after controlling for non-verbal IQ. Zero-order Pearson correlation coefficient \(r = .60, p < .001\), partial correlation controlled for RPM \(r = .61, p < .001\). Hollow circles – healthy controls, filled circles - patients.
A significant positive association was observed between the Expressive Language Index scores and the signal intensity change during Covert Articulation within three distinct clusters in both the patients and healthy controls. The largest cluster, occupying 1310 voxels ($35370 \text{ mm}^3$), was located within the right precuneus and posterior division of the right cingulate gyrus. The second cluster, containing 1227 voxels ($33129 \text{ mm}^3$), was located in the vicinity of the right frontal pole, right paracingulate gyrus and right superior frontal gyrus. The third, smallest cluster of 514 voxels ($13872$) was located in the vicinity of the right middle frontal gyrus (Table 4.6, Figure 4.15). Interaction contrasts did not reveal any statistically significant clusters, meaning that the strength of the association between the ELI and the BOLD signal change during the Covert Articulation task was the same for both the patients and healthy controls.

As previously, the values of the percentage change in signal intensity were extracted from the centres of gravity (COGs) of the detected clusters for all of the participants. The relationships with ECI indices were further quantified first without and then with the adjustment for non-verbal IQ (Table 4.7).

**Cluster 1**

Before the adjustment for non-verbal IQ, it was found that ELI explained 14% of the variation in signal within the COG of Cluster 1 ($F(1,34) = 5.5, p = .03, R^2 = .14, R^2_{\text{Adjusted}} = .14$). Thus, ELI significantly predicted a change in signal within the COG of Cluster 1 ($r = .37, t (35) = 2.35, p = .03$). Following the adjustment for non-verbal IQ, the effect of ELI was no
Table 4.6
Clusters where a change in signal during the Covert Articulation condition was significantly predicted by the Expressive Language Index CELF-5 score

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>N of voxels</th>
<th>p*</th>
<th>Max Z-stat value</th>
<th>Max Z-stat voxel</th>
<th>Centre of gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>Centre of gravity</td>
<td>Anatomical location (probability)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>y</td>
<td>Coordinates</td>
<td>Anatomical location (probability)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>z</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1310</td>
<td>6.91e−06</td>
<td>3.99</td>
<td>4</td>
<td>89% Right Precuneus Cortex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-62</td>
<td>52</td>
<td>87% Right Frontal Pole</td>
</tr>
<tr>
<td>2</td>
<td>1227</td>
<td>1.38e−05</td>
<td>3.8</td>
<td>16</td>
<td>87% Right Frontal Pole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>38</td>
<td>12% Right Middle Frontal Gyrus, 2% Right Superior Frontal Gyrus</td>
</tr>
<tr>
<td>3</td>
<td>514</td>
<td>.0129</td>
<td>3.55</td>
<td>30</td>
<td>12% Right Middle Frontal Gyrus, 2% Right Superior Frontal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>38</td>
<td>12% Right Middle Frontal Gyrus, 2% Right Superior Frontal Gyrus</td>
</tr>
<tr>
<td><strong>Negative association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p* Corrected for familywise error.
Coordinates in MNI space, anatomical location according to Harvard-Oxford cortical structural atlas


longer statistically significant. The model explained 14.8% of the variation in signal within the COG of Cluster 1 ($F(2, 33) = 2.87$, $p = .07$, $R^2 = .15$, $R^2_{Adjusted} = .10$). ELI was no longer predictive of a change in signal within the COG of Cluster 1 ($r = .30$, $t(35) = 1.43$, $p = .16$). The unstandardised $B$ – coefficient reduced by more than 10% (from .008 to .006), implying that RPM was an important confounder.
Figure 4.15. Areas where a change in signal during the Covert Articulation condition was significantly predicted by the Expressive Language Index CELF-5 score. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Table 4.7
Predictive value of ELI on activation during the Covert Articulation condition in the COGs of the clusters detected by whole-brain voxel-wise analyses, before and after the adjustment for non-verbal IQ

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Without the adjustment for non-verbal IQ</th>
<th>Without the adjustment for non-verbal IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EV</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>ELI</td>
<td>.008 (.001 to .015)</td>
</tr>
<tr>
<td></td>
<td>RPM</td>
<td>.002 (-.004 to .007)</td>
</tr>
<tr>
<td>2</td>
<td>ELI</td>
<td>.008 (.005 to .012)</td>
</tr>
<tr>
<td></td>
<td>RPM</td>
<td>-.001 (-.004 to .002)</td>
</tr>
<tr>
<td>3</td>
<td>ELI</td>
<td>.005 (.024e-2 to .009)</td>
</tr>
<tr>
<td></td>
<td>RPM</td>
<td>-.003 (-.007 to .021e-2)</td>
</tr>
</tbody>
</table>

Cluster refers to clusters described in Table 4.6
EV – Explanatory variable
B – Slope (estimated percentage increase in signal intensity per one ELI or RPM score point increase)
95% CI – 95% confidence interval for the slope
r - standardised residual
R²a – Adjusted coefficient of determination, indicating proportion in signal variance, explained by the model
ELI – Expressive Language Index
RPM – Raven’s Progressive matrices

Cluster 2

Before the adjustment for non-verbal IQ, it was found that ELI explained 38% of the variation in signal within the COG of Cluster 2 (F(1,33) = 19.85, p < .001, R² = .38, R²Adjusted = .36). Thus, ELI significantly predicted a change in signal within the COG of Cluster 2 (r = .61, t (34) = 4.46, p < .001). Following the adjustment for non-verbal IQ, the effect of ELI remained statistically significant. The model explained 38.3%
of the variation in signal within the COG of Cluster 2 \( (F(2, 32) = 9.92, p < .001, R^2 = .38, R^2_{\text{Adjusted}} = .34) \). ELI remained predictive of a change in signal within the COG of Cluster 2, irrespective of non-verbal cognitive ability \( (r = .68, t(34) = 3.80, p = .001) \) (Figure 4.16). The unstandardised B – coefficient in this case increased from .008 to .009, implying that RPM was not an important confounder.

**Cluster 3**

Before the adjustment for non-verbal IQ, it was found that ELI explained 11.8% of the variation in signal within the COG of Cluster 3 \( (F(1,34) = 4.57, p = .04, R^2 = .12, R^2_{\text{Adjusted}} = .09) \). Thus, in a simple regression model, ELI significantly predicted a change in signal within the COG of Cluster 3 \( (r = .34, t(35) = 2.14, p = .04) \). Following the adjustment for non-verbal IQ, the effect of ELI remained statistically significant. The model explained 20.6% of the variation in signal within the COG of Cluster 3 \( (F(2, 33) = 4.29, p < .02, R^2 = .21, R^2_{\text{Adjusted}} = .16) \). ELI remained predictive of a change in signal within the COG of Cluster 3, irrespective of non-verbal cognitive ability \( (r = .59, t(35) = 2.93, p = .006) \) (Figure 4.17). The unstandardised B – coefficient in this case increased from .005 to .008 implying that RPM was not an important confounder.

### 4.3.4 Cerebellar analyses in healthy controls: metabolic activity associated with the Semantic Retrieval and Covert Articulation conditions

For the contrast Semantic Retrieval > Covert Articulation, one cluster comprised of 10553 voxels was detected where response exclusive to the Semantic Retrieval condition has occurred. The cluster extended into both cerebellar
Figure 4.16. Illustration of the significant predictive relationship between ELI and mean percentage signal change within the centre of gravity (COG) of Cluster 2 during the Covert articulation condition, the relationship remained significant after controlling for non-verbal IQ. Zero-order Pearson correlation coefficient $r = .61$, $p < .001$; partial correlation controlled for RPM $r = .56$, $p = .001$. Hollow circles – healthy controls, filled circles - patients

Figure 4.17. Illustration of the significant predictive relationship between ELI and mean percentage signal change within the centre of gravity (COG) of Cluster 3 during the Covert articulation condition, the relationship remained significant after controlling for non-verbal IQ. Zero-order Pearson correlation coefficient $r = .34$, $p = .04$; partial correlation controlled for RPM $r = .45$, $p = .006$. Hollow circles – healthy controls, filled circles - patients
hemispheres, with the centre of gravity located in the vicinity of the Crus VI and VIIb of the vermis and Right lobule V, and maximum intensity voxel located in the vicinity of the Right lobule VI (Table 4.8, Figure 4.18).

A single but much smaller cluster of voxels within the cerebellum was detected where change in signal was associated exclusively with the Covert Articulation condition. Both the centre of gravity and maximum intensity voxel were located within right cerebellar hemisphere, Crus II and I (Table 4.8, Figure 4.19).

Table 4.8
Areas within the cerebellum where change in signal was exclusively associated with Semantic Retrieval condition (Semantic Retrieval > Covert Articulation contrast) and Covert Articulation condition (Covert Articulation > Semantic Retrieval contrast) in Healthy controls

<table>
<thead>
<tr>
<th>Cluster index</th>
<th>N of voxels</th>
<th>p*</th>
<th>Max Z-stat value</th>
<th>Coordinates</th>
<th>Anatomical location (probability)</th>
<th>Coordinates</th>
<th>Anatomical location (probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td></td>
</tr>
<tr>
<td>Semantic Retrieval &gt; Covert Articulation</td>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td>10.4</td>
<td>5.62E-29</td>
<td>9% Right VI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-48</td>
<td></td>
<td></td>
<td>-62.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-16</td>
<td></td>
<td></td>
<td>-24.7</td>
</tr>
<tr>
<td>Covert Articulation &gt; Semantic Retrieval</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>5.3</td>
<td>0.0005</td>
<td>84% Right Crus II, 16% Right Crus I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-80</td>
<td></td>
<td>58</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-38</td>
<td></td>
<td></td>
<td>-39.5</td>
</tr>
</tbody>
</table>

*Corrected for familywise error.

Coordinates in MNI space, anatomical location according to Cerebellar Atlas in MNI152 space, normalised with FLIRT.
Figure 4.18. Areas of the cerebellum where response is associated exclusively with Semantic Retrieval. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Figure 4.19. Areas of the cerebellum where metabolic response is associated exclusively with Covert Articulation. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space
4.3.5 Analyses of the haemodynamic response within a-priori defined ROIs: a three-way mixed ANOVA

A three-way mixed ANOVA with the condition (Semantic Retrieval, Covert Articulation); ROI (L-BA, L-WA, L-GA, R-BA, R-WA, R-GA) as the within-subject factor and the group (patients, healthy controls) as the between-subject factor was performed in order to examine the factors affecting the percentage change in signal within the specified regions during the in-scanner task performance.

Prior to running the ANOVA, the data were tested for normality using the Shapiro-Wilk test. The scores were normally distributed in all of the ROIs except the Left Geschwind Area. On examination, three outlier scores beyond three standard deviations of the mean were detected in this area in the Semantic Retrieval condition (two in the healthy control group and one in the patient group). Three further outlier scores were detected in this area within the Covert Articulation condition (two in the patient group and one in the healthy control group). After removing these extreme scores from the dataset, the Shapiro-Wilk test was performed again and the data were shown to be normally distributed (all $p > .05$). Levene’s test of equality of variances indicated that the variances were homogeneous for all levels of the repeated measures variables, making the data suitable for examination using parametric tests.

An important consideration for ANOVA is the sphericity of the data. This was violated for the Condition * ROI interaction effect ($\chi^2 (14) = 41.47$, $p < .001$); therefore the degrees of
freedom were corrected using a Greenhouse–Geisser correction (estimate of sphericity, $\epsilon = .61$) This correction was also applied to the three-way interaction effect of Condition * ROI * Group for the same reason.

### 4.3.5.1 Main effects of the group, condition and ROI

There was a non-significant main effect of Group, $F (1, 30) = .009, p = .92$, indicating that, when collapsed across conditions and ROIs, the overall change in signal intensity did not differ significantly between the patients ($M = -.01, SEM = .03$) and healthy controls ($M = -.01, SEM = .02$) (Figure 4.20)

![Figure 4.20](image)

*Figure 4.20. Main effect of Group, collapsed across ROIs and conditions. Both activation and de-activation were observed across subjects in both groups, with no significant between-group differences*

There was also a non-significant main effect of Condition, $F (1, 30) = .007, p = .94$, indicating that, when collapsed across ROIs and groups, the change in signal intensity did not differ significantly between the Semantic Retrieval ($M = -.01, SEM = .02$) and Covert Articulation ($M = -.01, SEM = .02$)
conditions (Figure 4.21). There was a significant main effect of ROI, $F(5, 150) = 10.66, p < .001$, indicating that, when collapsed across groups and conditions, the change in signal intensity varied, depending on the ROI. Descriptive statistics for the percentage change in signal intensity within the ROIs are presented in Table 4.9.

![Figure 4.21. Main effect of condition, collapsed across groups and ROIs. Both activation and de-activation were observed across conditions, with no significant difference between them](image)

<table>
<thead>
<tr>
<th>Region of interest (ROI)</th>
<th>Mean % signal change</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Broca’s area (L-BA)</td>
<td>.03</td>
<td>.04</td>
</tr>
<tr>
<td>Left Wernicke’s area (L-WA)</td>
<td>-.02</td>
<td>.03</td>
</tr>
<tr>
<td>Left Geschwind’s area (L-GA)</td>
<td>-.07</td>
<td>.03</td>
</tr>
<tr>
<td>Right Broca’s area (R-BA)</td>
<td>.11</td>
<td>.04</td>
</tr>
<tr>
<td>Right Wernicke’s area (R-WA)</td>
<td>.07</td>
<td>.04</td>
</tr>
<tr>
<td>Right Geschwind’s area (R-GA)</td>
<td>-.16</td>
<td>.03</td>
</tr>
</tbody>
</table>

SEM – standard error of the mean
Post-hoc Bonferroni-corrected pairwise comparisons were carried out between the corresponding ROIs in both hemispheres (L-BA/R-BA, L-WA/R-WA, L-GA/R-GA) and no statistically significant differences were found (Figure 4.22). This suggests that the source of the significant interaction was in the differences between non-corresponding regions, which has limited relevance for the interpretation of the results.

![Figure 4.22. Main effect of ROIs, collapsed across groups and conditions. Activation was observed in L-BA, R-BA and R-WA, de-activation in L-GA and R-GA, and both activation and de-activation across subjects in L-WA. No significant differences were observed between the signal changes in the corresponding regions (L-BA/R-BA, L-WA/R-WA, L-GA/R-GA)](image-url)
4.3.5.2 Two-way interaction effects: Condition *Group, Condition*ROI and Group*ROI

**Condition*Group interaction**

This interaction effect informs whether a change in BOLD signal in either group varies as a function of the task condition. There was no significant interaction effect between Group and Condition, $F (1, 30) = 0.90$, $p = .19$, suggesting that, when collapsed across ROIs, there was no significant difference in the percentage signal change in different groups, based on the condition they were in (Figure 4.23). Descriptive statistics for the interaction are presented in Table 4.10.

![Figure 4.23. Two-way Condition*Group interaction, collapsed across ROIs. White bars – healthy controls, grey bars – patients. Two bars on the left: Both activation and de-activation were observed during the Semantic Retrieval in both groups, with no statistical differences. Two bars on the right: Both activation and de-activation were observed during Covert Articulation in both groups, with no statistical differences](image-url)
Table 4.10
*Signal intensity change in the healthy controls and patients during the Semantic Retrieval and Covert Articulation, collapsed across ROIs

<table>
<thead>
<tr>
<th>Group*Condition</th>
<th>Mean % signal change</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls*Semantic Retrieval</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Healthy controls*Covert Articulation</td>
<td>-.03</td>
<td>.03</td>
</tr>
<tr>
<td>Patients*Semantic Retrieval</td>
<td>-.02</td>
<td>.03</td>
</tr>
<tr>
<td>Patients*Covert Articulation</td>
<td>.01</td>
<td>.03</td>
</tr>
</tbody>
</table>

SEM – standard error of the mean

Condition*ROI interaction

This interaction effect reveals whether the signal change is different for the defined ROIs, depending on which task condition is being performed. There was a significant interaction effect between Condition and ROI, \( F(3.06, 91.85) = 8.24, p < .001 \), suggesting that the percentage change in signal differed significantly between the ROIs, depending on the task condition. Descriptive statistics for the Condition*ROI are presented in Table 4.11.

Table 4.11
*Signal change in ROIs split by condition and collapsed across groups

<table>
<thead>
<tr>
<th>Condition*ROI</th>
<th>Mean % signal change</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic Retrieval*Left Broca’s area (L-BA)</td>
<td>.10</td>
<td>.05</td>
</tr>
<tr>
<td>Semantic Retrieval*Left Wernicke’s area (L-WA)</td>
<td>-.05</td>
<td>.04</td>
</tr>
<tr>
<td>Semantic Retrieval*Left Geschwind’s area (L-GA)</td>
<td>-.08</td>
<td>.03</td>
</tr>
<tr>
<td>Semantic Retrieval*Right Broca’s area (R-BA)</td>
<td>.16</td>
<td>.05</td>
</tr>
<tr>
<td>Semantic Retrieval*Right Wernicke’s area (R-WA)</td>
<td>.06</td>
<td>.04</td>
</tr>
<tr>
<td>Semantic Retrieval*Right Geschwind’s area (R-GA)</td>
<td>-.25</td>
<td>.04</td>
</tr>
<tr>
<td>Covert Articulation*Left Broca’s area (L-BA)</td>
<td>-.04</td>
<td>.05</td>
</tr>
<tr>
<td>Covert Articulation*Left Wernicke’s area (L-WA)</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Covert Articulation*Left Geschwind’s area (L-GA)</td>
<td>-.07</td>
<td>.03</td>
</tr>
<tr>
<td>Covert Articulation*Right Broca’s area (R-BA)</td>
<td>.05</td>
<td>.03</td>
</tr>
<tr>
<td>Covert Articulation*Right Wernicke’s area (R-WA)</td>
<td>.07</td>
<td>.04</td>
</tr>
<tr>
<td>Covert Articulation*Right Geschwind’s area (R-GA)</td>
<td>-.08</td>
<td>.03</td>
</tr>
</tbody>
</table>

SEM – standard error of the mean
Post-hoc Bonferroni-adjusted pairwise comparisons were performed for both conditions between corresponding regions in the left and right hemispheres. A significant difference in haemodynamic response was found between L-GA and R-GA during the Semantic Retrieval (Table 4.12, Figure 4.24).

Table 4.12

<table>
<thead>
<tr>
<th>Pairwise comparison</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic Retrieval: L-BA vs R-BA</td>
<td>-1.46</td>
<td>35</td>
<td>.15</td>
</tr>
<tr>
<td>Semantic Retrieval: L-WA vs R-WA</td>
<td>-1.18</td>
<td>35</td>
<td>.08</td>
</tr>
<tr>
<td>Semantic Retrieval: L-GA vs R-GA</td>
<td>4.28</td>
<td>32</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Covert Articulation: L-BA vs R-BA</td>
<td>-2.13</td>
<td>35</td>
<td>.04</td>
</tr>
<tr>
<td>Covert Articulation: L-WA vs R-WA</td>
<td>-1.78</td>
<td>35</td>
<td>.08</td>
</tr>
<tr>
<td>Covert Articulation: L-GA vs R-GA</td>
<td>.41</td>
<td>32</td>
<td>.68</td>
</tr>
</tbody>
</table>

*significant at Bonferroni-adjusted critical significance level p = .008

Figure 4.24. Two-way Condition*ROI interaction, collapsed across groups. White bars – Semantic Retrieval, grey bars – Covert Articulation. Both activation and de-activation were observed across tasks and ROIs. The source of the significant interaction effect lies in the difference between L-GA and R-GA during Semantic Retrieval: both areas displayed a drop in signal, but this was significantly more pronounced in the R-GA.
Chapter 4

**Group*ROI interaction**

This interaction effect provides information on whether the BOLD signal change in either group changes as a function of the ROI localisation. There was no significant interaction between Group and ROI, $F(5, 150) = .57, p = .72$, indicating that the percentage signal change was not significantly different between the groups in any of the ROIs, when collapsed across conditions (Figure 4.25). Descriptive statistics for the interaction are presented in Table 4.13.

*Figure 4.25.* Two-way ROI*Group interaction, collapsed across conditions. White bars – healthy controls, grey bars – patients. Both activation and de-activation were observed across Groups and ROIs, with no significant differences between corresponding pairs (e.g. patients’ L-BA vs healthy controls L-BA).
### Table 4.13
*Signal change in Groups split by ROI and collapsed across conditions*

<table>
<thead>
<tr>
<th>Group*ROI</th>
<th>Mean % signal change</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls*Left Broca’s area (L-BA)</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Healthy controls*Left Wernicke’s area (L-WA)</td>
<td>-0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Healthy controls*Left Geschwind’s area (L-GA)</td>
<td>-0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Healthy controls*Right Broca’s area (R-BA)</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Healthy controls*Right Wernicke’s area (R-WA)</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Healthy controls*Right Geschwind’s area (R-GA)</td>
<td>-0.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients*Left Broca’s area (L-BA)</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients*Left Wernicke’s area (L-WA)</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients*Left Geschwind’s area (L-GA)</td>
<td>-0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients*Right Broca’s area (R-BA)</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients*Right Wernicke’s area (R-WA)</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients*Right Geschwind’s area (R-GA)</td>
<td>-0.14</td>
<td>0.05</td>
</tr>
</tbody>
</table>

SEM – standard error of the mean

#### 4.3.5.3 Three-way interaction effect: group*condition* ROI

This interaction effect demonstrates how a signal change in a given ROI changes as a function of both task condition and group belonging. The three-way interaction between Group, Condition and ROI was not statistically significant, $F (3.06, 91.85) = 2.03, p = .11$, meaning that the percentage signal change did not differ between the groups when separated by ROI and conditions (Figure 4.26). Descriptive statistics for the interaction terms are presented in Table 4.14.
Figure 4.26. Three-way Condition*ROI* Group interaction. White bars – healthy controls, grey bars – patients. Both activation and de-activation were observed across groups, conditions and ROIs. However, there were no significant differences between corresponding pairs (e.g., L-BA activation during Semantic retrieval in patients and controls).
<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>ROI</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Left Broca’s area</td>
<td>.14</td>
<td>.07</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Left Wernicke’s area</td>
<td>-.06</td>
<td>.05</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Left Geschwind’s area</td>
<td>-.11</td>
<td>.04</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Right Broca’s area</td>
<td>.17</td>
<td>.07</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Right Wernicke’s area</td>
<td>.14</td>
<td>.06</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Semantic Retrieval</td>
<td>Right Geschwind’s area</td>
<td>-.25</td>
<td>.05</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Left Broca’s area</td>
<td>-.03</td>
<td>.06</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Left Wernicke’s area</td>
<td>-.04</td>
<td>.04</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Left Geschwind’s area</td>
<td>-.07</td>
<td>.03</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Right Broca’s area</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Right Wernicke’s area</td>
<td>.03</td>
<td>.05</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Covert Articulation</td>
<td>Right Geschwind’s area</td>
<td>-.12</td>
<td>.04</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Left Broca’s area</td>
<td>.06</td>
<td>.07</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Left Wernicke’s area</td>
<td>-.04</td>
<td>.06</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Left Geschwind’s area</td>
<td>-.05</td>
<td>.05</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Right Broca’s area</td>
<td>.15</td>
<td>.08</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Right Wernicke’s area</td>
<td>-.02</td>
<td>.07</td>
</tr>
<tr>
<td>Patients</td>
<td>Semantic Retrieval</td>
<td>Right Geschwind’s area</td>
<td>-.24</td>
<td>.06</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Left Broca’s area</td>
<td>-.04</td>
<td>.07</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Left Wernicke’s area</td>
<td>.05</td>
<td>.05</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Left Geschwind’s area</td>
<td>-.06</td>
<td>.04</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Right Broca’s area</td>
<td>.02</td>
<td>.05</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Right Wernicke’s area</td>
<td>.12</td>
<td>.06</td>
</tr>
<tr>
<td>Patients</td>
<td>Covert Articulation</td>
<td>Right Geschwind’s area</td>
<td>-.05</td>
<td>.05</td>
</tr>
</tbody>
</table>

SEM – standard error of the mean
4.4 Discussion

4.4.1 Similarities and differences in the task-related activation between the patients and controls

The present study investigated the hypothesis that brain metabolic response during language processing will differ between patients that have sustained PFT in childhood and healthy volunteers. An fMRI task was employed with two distinct, but related conditions; they shared the covert articulation element of the highly rehearsed words, but differed in the amount of semantic load.

4.4.1.1. Increased involvement of motor-regulating regions in patients during Semantic Retrieval

The group-average activation maps were contrasted to reveal the regions where the change in BOLD signal was statistically different between the patients and controls. In the Semantic Retrieval condition such contrasting revealed a cluster within the right hemisphere where the healthy controls exhibited a more prominent response. Importantly, this does not necessarily mean that the response in either group reached an above-threshold level, but instead reflects a statistically significant difference in the signal change between the two groups. Such a difference was observed in the Right Postcentral and Precentral gyri, key structures forming primary somatosensory and motor cortices (Haines, 2004). We can speculate that the Post-Central gyrus response is most likely to be associated with the sensation of the button box, held by the participants in the scanner.

Conversely, inter-group contrasting of the covert articulation
activation maps did not reveal any statistically significant clusters, demonstrating that there was no difference in the amount of haemodynamic response during simple articulation of the words. This suggests that speech articulation is facilitated and processed in a similar manner, and the only statistically significant differences in metabolic response occurred during the Semantic Retrieval condition, but not during the covert articulation. Since both conditions share the word articulatory planning component, the difference can be attributed to the processing of the meaning (semantics), indicating variations in higher level language abilities between the groups.

4.4.1.2 Key areas of the the perisylvian language network respond bilaterally and comparably in patients and healthy controls

In addition to the whole-brain analyses, we also used an a-priori defined ROI approach to investigate the differences in metabolic response within the perisylvian regions, forming the canonical language support network, namely the bilateral Broca’s, Wernicke’s and Geschwind’s areas. Contrary to expectations, there was no statistical effect of group, suggesting that the response was comparable, although the dispersion of the individual percentage signal change scores around the means was greater in the patients. This offers further evidence in regard to the qualitative similarities in language processing between the groups, with increased variability in the patients, which resonates with the earlier findings from the neuropsychological study and analysis of the whole-brain activation maps.

One of the hypotheses for the study was that Wernike’s and Geschwind’s areas would show a change in response during the semantic retrieval, but not in the articulation of speech. This
hypothesis was partially supported; there was greater deactivation of the R-GA compared to the L-GA in the Semantic Retrieval condition. No differences were detected between the L-BA and R-BA, or the L-WA and R-WA. Geschwind’s territory is located in the inferior parietal lobe and was proposed as an addition to the original Broca-Wernicke’s model, as an area that is important for cross-modal, cortico-cortical associations, underpinning higher cognitive functions, including the semantics of language (Geschwind, 1970; Aboitiz, García, Brunetti, & Bosman, 2006). However, this significant difference disappeared when L-GA and R-GA comparisons were made for each group separately. Considering the small sample size, it is difficult to judge whether the observed significance was a valid or spurious finding, and this can only be validated with a larger sample size. On balance, the ROI analyses revealed no difference in the way in which the patients and controls recruited key regions of the perisylvian language network, and equal involvement of both hemispheres during the Semantic Retrieval and Covert Articulation, contrary to the prevalent view of left-side language dominance (Froest et al., 1999; Knecht et al., 2000).

4.4.2 Predictive values of overt language performance on the changes in BOLD signal

As a separate strand of analysis in the present study, regression modelling was applied to examine whether language performance outside of the scanner was predictive of the BOLD signal fluctuations during associated task processing. Several distinct regions were observed where activation was predicted by overt language performance, remaining statistically significant even after controlling for
non-verbal IQ. This demonstrates that reliable inferences can be made about brain functioning based on neuropsychological investigation alone. In addition, this finding adds to the body of literature describing the language-supporting architecture, beyond the classical Broca-Wernicke-Geschwind model.

4.4.2.1 LCI, a measure of semantic processing, predicts metabolic response on the border of the left angular gyrus and occipital lobe

The Language Content Index (LCI) is a behavioural measure most closely related to the Semantic Retrieval task. It takes into account various aspects of semantic processing, such as concept and category awareness, comprehension of associations and relationships between words, the interpretation of factual and inferential information, and vocabulary development (Wiig et al., 2013). When non-verbal IQ was controlled for, the LCI standardised score was positively predictive of a change in BOLD response in a cluster of voxels on the border of the left lateral occipital cortex and angular gyrus. This region, as part of the perisylvian network, has long been implicated in a range of language-related functions (Price, 2012; Seghier, 2013), including semantic decisions about words and pictures (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996), phonological decisions (Démonet, Price, Wise, & Frackowiak, 1994), and speech comprehension (Homae, Hashimoto, Nakajima, Miyashita, & Sakai, 2002; Schmithorst, Holland, & Plante 2006). For the first time, we demonstrate that neuropsychological language assessment can be used as a reliable predictor of metabolic activity in this key language processing region.
4.4.2.2 ELI, a measure of language production, predicts metabolic response in the regions of the right hemisphere, including frontal pole, paracingulate gyrus superior frontal gyrus and middle frontal gyrus

The Expressive Language Index (ELI) is a measure of language production skills and is assessed using sentence assembly, formulation and recall tests (Wiig et al., 2013). When used as a regressor in the covert articulation condition, the ELI score was positively predictive of a response in two clusters located in the vicinity of the right frontal pole, the right paracingulate gyrus, the right superior frontal gyrus and the right middle frontal gyrus.

The contribution of the right hemisphere to language processing, in particular its frontal regions, is still not completely understood. For a long time, it has been viewed as a ‘reserve’ resource, utilised in the language recovery process when the left hemisphere is damaged (Basso, Gardelli, Grassi, & Mariotti, 1989; Heis & Thiell, 2006, Anglade, Thiel, & Ansaldo, 2014). However, recent decades have seen many studies emerging that have investigated the involvement of the right hemisphere in various aspects of language processing in a healthy population. Speech production, in particular, has been found to draw on right-hemispheric support (Silbert, Honey, Simony, Poeppel, & Hasson, 2014; Alexandrou, Saarinen, Mäkelä, Kujala, & Salmelin, 2017). Adding to the emerging body of evidence, our study demonstrates that right hemispheric involvement in speech production can be reliably predicted by overt expressive language performance.

Importantly, when both LCI and ELI were used as predictors, the range of signal change values surpassed a zero mark.
(Figures 4.14, 4.17 and 4.17), meaning that both an increase and a decrease in signal intensity were observed. Higher language scores were associated with the most activation, while lower language scores were associated with the most deactivation. This illustrates an important point, which is that assessing the involvement of neural structures in language processes, based simply on detecting a signal above a set arbitrary threshold, may not be the most informative approach. Both deactivation and activation in the same region can reflect the degree of engagement of a given area in the task of interest.

**4.4.3 Cerebellar involvement in language processing: vermal and right-hemispheric activation**

Further exploratory investigation was made into the metabolic response patterns within the cerebellum of the healthy control group. In the patient group, this type of analysis was not possible due to the irregular anatomy of their posterior fossa and image registration difficulties. Nevertheless, important information was generated with regard to specific regions of the cerebellum involved in the task processing, damage to which may expose the PFT patients to potential language deficits.

Activation exclusive to the Covert Articulation condition was observed in a small cluster in the vicinity of Crus I and Crus II of the right cerebellar hemisphere. According to the currently prevailing understanding of the cerebellar functional topography there is a distinction between the structures supporting motor control vs cognitive and affective processes (Stoodley & Schmahmann, 2010; Marien et al., 2014), with speech articulation being supported by the midline/paravermal
cerebellar regions. For example, it has previously been shown that medial lobule VI responds during speech articulation (Thurling et al., 2011), while damage to the midline and paravermal regions at the level of lobules V to VII in post-stroke patients has been associated with symptoms of dysarthria (Ackermann, Vogel, Petersen, & Poremba, 1992; Urban et al., 2003; Richter et al., 2007). In the current fMRI task, both condition shared speech articulation component which may be the reason why on contrasting we were not able to observe significant difference in activation in these areas. Crucially, however, our finding suggests that the role of the right cerebellar hemisphere in the articulation of speech is not currently fully appreciated.

Activation unique to the Semantic Retrieval condition was substantially more widespread and extended into both cerebella hemispheres. The centre of gravity was located in the vicinity of the Crus VI and VIIb of the vermis and Right lobule V, while the maximum intensity voxel located in the vicinity of the Right lobule VI. These findings are largely in line with the current knowledge. Previously, it has been shown that Crus I and Crus II of the right lateral cerebellar lobules VI-VII have been implicated in aspects of language processing where access to semantics is required, such as word generation, word stem completion and semantic processing (Stoodley and Schmahmann, 2009; Marien et al., 2014). Our results suggest that medial cerebellar structures also play important role in the processing of the semantics, although they are more commonly discussed in the context of speech production, as explained above.

The findings from the cerebellar analyses potentially have important implications for this field of research. Notably, they
may help settle the disagreement in the behavioural literature regarding the presence of long-term post-PFT speech and language impairments. It may be that inconsistencies arise due to differences in the specific cerebellar sites injured by tumours and their treatment. Unless the damage extends to the highlighted structures, it is possible that language function will be preserved. It is important, therefore, that the tumour site is taken into account when assessing patients’ risk for developing language disturbances, along with more commonly used risk factors such as tumour type or treatment regimen. The same aspects of tumour location may also become relevant when when it comes to stratification of the specific language deficits arising post-treatment. Seeing that there may be difference in the areas that support exclusively articulation or semantic access, different injury site may contribute to the development of the deficits in either of two domains, although this hypothesis requires testing with a larger cohort of patients.

4.4.4 Limitations of the study

Several limitations must be considered when interpreting the outcomes of the present investigation. One specific issue of concern is the mode of the participants’ response. Sub-vocal, rather than overt, responses were utilised purely for methodological reasons; speaking aloud in the scanner is likely to result in unwanted head movement and additional respiratory activity, leading to motion artefacts. Thus, covert speech has predominantly been utilised in fMRI research of language (Huang, Carr, & Cao, 2001). However, studies have shown that covert and overt speech result in slightly different cortical activation patterns. Dogil et al. (2002), for instance, demonstrated that overt speech results in more widespread bilateral activation in both the cerebral and cerebellar cortices. Thus, it is likely that the observed activation patterns may not
fully reflect the complexity of the neural networks supporting natural overt speech production. However, at present, this is the best possible way of investigating speech processes with fMRI without inducing excess movement artefacts.

The validity of language fMRI findings has also been questioned in the literature on the grounds of the differences between on-demand and spontaneous language processing (Silbert, Honey, Simony, Poeppel, & Hasson, 2014; Hurlburt, Alderson-Day, Kühn, & Fernyhough, 2016). Arguably, on-demand task performance requires significant attentional input. For example, in our study, we consistently observed an increase in BOLD signal within the cingulate and paracingulate gyri. These structures have been implicated in executive function and attentional control (Paus, Koski, Caramanos, & Westbury, 1998; Fornito et al., 2004). Thus, in order to reliably separate speech and language metabolic activity from attentional control activity, future studies should include control conditions with attentional but not linguistic load.

Finally, analysis of the activation within the deep cerebellar nuclei was not possible due to the 3T MRI scanner having insufficient spatial resolution capabilities. Yet, these structures, in particular the dentate nucleus, are the key elements of the cortico-cerebellar loop, underpinning a range of linguistic and cognitive functions (Dum & Strick, 2003). In order to spatially resolve these small structures, high-field strength 7T MRI equipment has successfully been utilised (e.g., Diedrichsen et al., 2011; Thurling et al., 2012). This approach must be considered should similar studies be performed in the future, in order to construct a more
A comprehensive picture of the involvement of cerebellar structures in covert articulation and semantic retrieval.

4.4.5 Conclusions

In conclusion, the present study provides a novel insight into the long-term changes in the neural processing of language in PFT survivors. The methodological approach of language task-based fMRI has not been used previously in this group of patients. Thus, the present investigation offers a unique angle of evidence in the debate, which has so far been mainly informed by behavioural studies.

The present study has convincingly demonstrated that, despite no direct damage to the supra-tentorial areas, PFT survivors display deviations from normality in terms of the metabolic processing of language-based tasks. Specifically, patients lacked BOLD response in the number of areas during semantic processing. At the same time, a number of similarities were observed between patients and controls including in the response of the perisylvian regions of interest. In addition, the behavioural measures of language were equally accurate in predicting the metabolic response for the patients and controls. The behavioural measure of semantic access predicted a signal change on the border of the left occipital lobe/angular gyrus. The behavioural measure of expressive language predicted a signal change in the regions of the right hemisphere: the frontal pole, paracingulate gyrus, superior frontal gyrus and middle frontal gyrus.

In agreement with much of the published literature, we have demonstrated that the midline/paravermal and right cerebellar areas may play a particularly important role in the preservation of the ability to articulate words and access language semantics.
Therefore, tumours affecting these areas may predispose patients to developing specific language-processing deficits.

Taken together, the findings demonstrate that the observed differences in language processing are quantitative rather than qualitative in nature. Resonating with the conclusions from the neuropsychological investigation, the present findings suggest that PFT sustained in childhood limits language processing capacity, although the underlying mechanisms of language processing remain unchanged. Patients and clinicians should be made aware of these prospects in order to facilitate the most appropriate post-treatment management.
Chapter 5: Global and tract-specific decline in white matter quality in PFT survivors

Key findings

- PFT survivors demonstrate widespread deterioration in their white matter quality, which is evident from the global decrease in the fractional anisotropy (FA) index, and the global increase in the mean (MD) and radial (RD) diffusivities;
- The FA index in the left-hemispheric structures, including the cortico-spinal tract, the anterior thalamic radiation, the superior longitudinal fasciculus and the inferior fronto-occipital fasciculus, positively predicts performance in terms of the measure of linguistic semantic access in patients;
- FA is significantly reduced in the bilateral arcuate fasciculi, a tract subserving perisylvian language network, with a larger effect size in the left hemisphere;
- MD, RD and AD are increased within the bilateral superior cerebellar peduncle in patients, a key segment of the dentato-thalamo-cortical tract, facilitating communication between the cerebellum and the cerebrum;
- No significant correlations were observed between FA, MD, RD or AD in any of the ROIs and CELF-5 index scores;
- All of the DTI metrics were comparable between the radiotherapy and non-radiotherapy subgroups of patients, except the FA within the left SCP, which was higher in the radiotherapy-treated patients.

5.1 Introduction

5.1.1 Role of the white matter in cognition and language processing

Complex cognitive functions rely on the coordinated activity of...
multiple cortical regions, according to the widely accepted connectionist accounts of cognition (Karmiloff-Smith, 1995). Neuronal axons, grouped in bundles of white matter tracts, facilitate signal exchange between the spatially distributed regions. Three classes of fibers are broadly defined, depending on the brain structures they connect. Association pathways facilitate the exchange of electrochemical signals between different parts of the same cerebral hemisphere. These include long-range fibers, such as the superior and inferior longitudinal fasciculi, the uncinate fasciculus, and the inferior fronto-occipital fasciculus, as well as short range U-fibers linking adjacent cortical areas. Commissural pathways connect different hemispheres, the largest and most important of which is the corpus callosum. Finally, projection pathways connect the cerebral cortex with the lower parts of the brain and spinal cord. Among these are the cortico-spinal tract, the thalamic radiation and the cortico-bulbar tract (Wakana, Jiang, Nagae-Poetscher, Van Zijl, & Mori, 2004).

In the late 19th century, neuroanatomists such as Meynert and Wernicke postulated that association and projection connection systems enable higher cognition and the performance of complex behaviours (Catani & Schotten, 2012). Consequently, damage to the white matter structures poses a direct risk to normal cognition. Indeed, numerous studies of disease and ageing-related neuronal injury have reported an association between adverse volumetric and microstructural white matter changes and cognitive impairments. For instance, in a study of 1077 elderly adults it was found that increase in the periventricular white matter lesion load correlated with the gradual decrease in all aspects of cognitive function, and particularly psychomotor speed.
which was almost 1SD below average in the patients with the most severe lesions (de Groot et al., 2000). In another representative study of patients with traumatic brain injury by Kraus et al. (2007) a moderate statistically significant relationship was detected between the white matter load (a number of ROIs with significantly decreased FA values compared to controls) and measures of memory and executive function (both \( r = -0.4 \)).

### 5.1.2 Basic principles of the DTI method

Until relatively recently, studying the white matter anatomy and pathways on a macroscale was achieved primarily using post-mortem investigations (Mori et al., 2005). The development of diffusion-weighted magnetic resonance imaging (DWI) enabled the study of the white matter microstructure in-vivo. This method allows for detecting the motion of the hydrogen protons within the tissue of interest, driven by the thermal energy carried by the water molecules. Unrestrained diffusion takes the form of random Brownian motion (Figure 5.1). Typically, water molecules move in the brain tissue at an approximate speed of 10 \( \mu \text{m} \) every 50 ms (Le Bihan et al., 2001).

![Figure 5.1](image.png)

*Figure 5.1. Diffusion-driven random motion of a single water molecule. Vector \( \mathbf{r} \) - molecular displacement, \( \Delta \) - time interval between \( t_0 \) and \( t_1 \). From (Hagmann et al., 2006).*
Tissue components such as cell membranes, macromolecules or fibers present obstacles to the molecules’ motion, resulting in diffusion anisotropy – preferential movement in a particular direction. In the white matter, diffusion is directionally restricted due to the close proximity and myelination of the axons (Baelieu, 2002). White matter tracts are typically organised as bundles of axons, running in parallel, facilitating faster diffusion in the direction of the fibers, and restricting water molecules’ movement perpendicular to the fibers. A higher degree of axonal myelination leads to increased anisotropy due to the reduction of the extracellular space (Figure 5.2).

**Figure 5.2.** Schematic diagram of the diffusion within the axonal bundles. Top panel: diffusion along the fibers; bottom panel: diffusion perpendicular to the fibers. Anisotropy increases with myelination. From (Voříšek & Syková, 1997).

In order to quantify the displacement of the hydrogen protons in the tissue with MRI, diffusion weighting is used, which involves the application of two controlled magnetic field gradient pulses in the MR sequences. Only those displacements that occur in the direction of the gradient become visible on the obtained contrasts (Le Bihan et al., 2001).
In the case of unrestricted, isotropic diffusion, the displacement can be characterised by a single parameter $D$, or diffusion coefficient. The diffusion coefficient, $D$ for water at 37°C is approximately $3 \cdot 10^{-9}$ m$^2$/sec (Hagmann et al., 2006). However, with directionally restricted (anisotropic) diffusion, a single parameter model is not sufficient, as the displacement is no longer equal in different directions. An alternative, diffusion tensor model, is a 3 x 3 x 3 matrix that characterises anisotropic diffusion in 3D space (Hagmann et al., 2006). It can be visualised as an ellipsoid, defined by the directions of the principle displacement vectors (eigenvectors), and their lengths (eigenvalues), (Figure 5.3).

![Diffusion tensor ellipsoid](image)

**Figure 5.3.** Diffusion tensor ellipsoid. The directions of the molecular displacement are defined by eigenvectors $\mathbf{v}_1$, $\mathbf{v}_2$ and $\mathbf{v}_3$ (left); the displacement distances are defined by eigenvalues $\lambda_1$, $\lambda_2$, $\lambda_3$ (right). The eigenvector corresponding to the largest eigenvalue ($\mathbf{v}_1$ and $\lambda_1$ respectively) defines the principal direction of diffusion. From (Mori, 2007).

Because tensors can be described mathematically as matrices, a number of useful scalars can be calculated. Typical indices derived from the DTI include axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA), (Hui, Cheung, Chan, & Wu, 2010). These
measures are derived using the following formulae:

AD simply equals the principle eigenvalue:

$$AD = \lambda_1$$

RD is the average of the remaining two eigenvalues:

$$RD = (\lambda_2 + \lambda_3)/2$$

MD is the average of the three eigenvalues combined:

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/3$$

Finally, FA describes the fraction of the magnitude of the tensor that can be explained by anisotropic diffusion:

$$FA = \sqrt{\frac{1}{2} \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

The diffusivity scalars (AD, RD and MD) are measured in micrometers per millisecond, while FA is the index and takes values between 0 and 1, with 1 being the perfect anisotropy. These measures allow for making inferences about the white matter integrity, orientational architecture and structural connectivity of the human brain. Often studies use FA as a primary measure of the structural WM integrity. In healthy, tightly packed fiber bundles there will be less intracellular space and more diffusion restriction, resulting in a higher FA index. However, FA is a non-specific measure and other scalars may be more useful when it comes to inferring the causes of microstructural abnormalities. For instance, mean diffusivity decreases with age due to the progressive myelination of the fibers; thus, MD can serve as a measure of WM maturation (Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010). At the same time, disease-related
neurodegeneration can adversely affect diffusion parameters. For example, progressive loss of myelin observed in multiple sclerosis leads to the increase in RD (Song et al., 2005), while axonal damage leads to the decrease in AD (Budde, Xie, Cross, & Song, 2009). Thus, using several scalars simultaneously can provide vital information not only about the state of the white matter, but also potential causes of any abnormalities.

5.1.3 Cerebro-cerebellar pathways

In recent years DTI has become a popular technique for investigating white matter changes in PFT survivors, mainly with the aim of explaining the mechanisms of post-treatment complications, such as posterior fossa syndrome and long-lasting cognitive deficits (e.g., Mabbott et al., 2006; Law et al., 2011; Rueckriegel et al., 2012; Palmer et al., 2012; Soelva et al., 2013). The technique has been useful in establishing a link between radiotherapy and white matter deterioration (Mulhern et al., 1999; Scantlebury et al., 2016), in particular within the frontal lobe (Qie et al., 2007), thus shedding light on the origins of the frequently reported cognitive dysfunction in PFT survivors.

The cerebo-cerebellar WM loop is a pathway of particular interest in this clinical group due to its proximity to the tumour site and the possibility of direct damage through surgical intervention (Pitsika & Tsitouras, 2013). The loop facilitates the reciprocal exchange of information between the cerebrum and cerebellum, and is further sub-divided into the efferent and afferent projections, which are also referred to as the dentato-thalamo-cortical (DTC) and cerebro-ponto-cerebellar (CPC) tracts. Ascending DTC projections
Chapter 5

originate in the dentate nucleus of the cerebellum, pass through the superior cerebellar peduncle, decussate in the rostral pons and midbrain, and via the ventral lateral nucleus of the thalamus project widely to cortical areas, including the language-associated regions (Figure 5.4).

Figure 5.4. 3D-rendered cerebro-cerebellar WM tract. From (Law et al., 2011)

Deterioration of the WM quality within the DTC tract has been investigated as a highly probable factor in the pathophysiology of post-operative mutism and posterior fossa syndrome, as well as cognitive decline in general. Several studies that have investigated this issue have reported adverse volumetric and structural changes within the whole DTC pathway (Law et al., 2011; Soelva et al., 2013; Oh et al., 2016), as well as within the local sites of passage, such as the superior cerebellar peduncle (Ojemann et al., 2013; Avula et
al., 2015; McEvoy et al., 2016), (Figure 5.5). For example, McEvoy et al. (2016) investigated white matter integrity within the DTC tract at the level of the superior cerebellar peduncle (SCP) in a group of PFT patients, stratified by the level of language functioning (intact, n = 19; mild deficit, n = 19 and posterior fossa syndrome, n = 9), (posterior fossa syndrome, in the context of this article, refers to cerebellar mutism post-surgery). They observed a reduction in FA within the bilateral SCP one year post-surgery in nine PFT patients who had developed cerebellar mutism. On the contrary, patients without posterior fossa syndrome did not exhibit this marker.

*Figure 5.5. Anatomy of the cerebellar peduncles. From (Nieuwenhuys, Voogd, & van Huijzen, 2008)*

**5.1.4 Language-implicated pathways**

With language being a primary focus of the present project, a DTI investigation would not be complete without considering the WM pathways implicated in language processing.
Language is one of the complex cognitive functions, supported by a distributed large-scale network of cortical regions and underlying white matter connections. The arcuate fasciculus, a sub-section of the superior longitudinal fasciculus, is one particular white matter pathway that has long been implicated in language processing (Catani and Jones, 2005; Rilling et al., 2008). Specifically, it is thought to facilitate signaling between the inferior frontal/precentral gyri (Broca’s territory), superior/medial temporal gyri (Wernike’s territory) and supramarginal/angular gyri (Geschwind’s territory) – the cortical areas comprising the canonical language support network (Figure 5.6). Thus, in line with the Wernike-Geschwind disconnection theory (Catani and Mesulam, 2008), adverse microstructural changes in this tract may be related to overt deficits in language functioning, in particular within the left hemisphere, in accordance with the classical theories of language lateralisation (Geva et al., 2015). To date, microstructural changes in the arcuate fasciculus have not been investigated in PFT survivors in relation to overt language deficits; thus, the present study is novel in this sense.

**Figure 5.6.** Tractography reconstruction of the arcuate fasciculus. Broca’s and Wernicke’s areas are connected by the direct (red) and indirect (yellow/green) WM pathways. From (Catani & Jones, 2005).
5.1.5 Aims and hypotheses

The main objective of the present study was to investigate whether the WM microstructure is altered in PFT survivors and how the changes are related to overt language abilities. The following aims were pursued:

- To compare DTI scalars, reflecting various properties of the microstructural integrity of the WM, between long-term PFT survivors and matched healthy controls;

- To assess the differences in the WM properties at the global (whole brain) and local (regions of interest) levels for the patients and healthy controls, as well as radiotherapy-treated and non-treated patients;

- To quantify the association between the DTI indices and CELF-5 language performance indices;

- To investigate the predictive value of WM integrity on overt language performance.

It was hypothesised that there would be deterioration in the WM quality in the PFT survivors compared to the healthy controls, which would be evident from the reduced FA and AD, and increased MD and RD. This would be observed both globally and within the superior cerebellar peduncles. Moreover, this deterioration would be more pronounced in the radiotherapy-treated patients, compared to those not treated with radiotherapy.

As language deficits were detected in the PFT survivors, it was also expected that the white matter integrity would be adversely affected in the arcuate fasciculus, a WM structure subserving perisylvian language region. It was expected that the DTI indices would correlate with the individual language
scores in this region. Specifically, based on the prior knowledge, it was expected that higher FA and AD values within the arcuate fasciculus will correspond to better performance on the CELF-5 indices, while lower MD and RD values will be detected in those with poorer language performance. Finally, it was hypothesised that the regression analyses would reveal specific regions where the WM structural integrity best predicted overt language performance.

5.2 Method

5.2.1 Diffusion-weighted imaging protocol

All of the MRI assessments were performed on a 3 Tesla Phillips MRI scanner using a 64 channel head coil. Diffusion weighted images were obtained by applying an Eco Planar Imaging (EPI) sequence with the following parameters: TR = 12000 ms, TE = 54.52 ms, matrix size 112 x 112 mm$^2$, 70 slices, slice thickness 2 mm, voxel size 2x2x2 mm, maximum diffusion weighting value b = 1000 s/mm$^2$, axial image orientation, aligned parallel to the anterior-posterior commissure. The scan time was around 6 minutes. MPRAGE ($T_1$-weighted image) was also obtained for anatomical guidance (TR = 8.1 ms, TE = 3.7 ms, TI = 960 ms, FOV - 25.6 X 25.6 mm$^2$, 256 x 256 mm$^2$ matrix, voxel size 1x1x1 mm, 160 slices).

5.2.2 Participants

Participants were recruited from the same cohort of subjects described in Chapter 3. Initially, 16 patients and 20 healthy controls were scanned. One patient and one healthy control dataset were removed following the data quality inspection. Details of the patients can be found in Table 5.1.
Using G*Power 3.9.1 software (Faul, Erdfelder, Lang & Buchner, 2007), it was determined that with the total obtained sample size of 34, the study would yield 56% power to detect a moderate effect size of .3, and 95% power to detect a large effect size of .5, assuming a one-tailed hypothesis and a critical significance level of .05. 80% power is the optimal recommended power for a clinical study (Suresh & Chandrashekara, 2012). Thus, for the present study’s findings to be considered reliable, the achieved effect sizes had to be in the large range (above .5). This is likely to be achievable, based on the previous related studies. For example, Mulhern et al. (1999) observed correlation coefficients between .44 and .56 in the investigation of the relationship between the white matter volume and cognitive performance indices. Soelva et al. (2013) reported reduced FA within the superior cerebellar peduncle in medulloblastoma and astrocytoma patients, compared to controls, yielding large effect sizes (Cohen’s $d > 1.1$ for both clinical groups).

**5.2.3 Procedure**

A diffusion-weighted scan was performed as part of the MRI assessment during research visit 2 (see schedule in Chapter 4, Table 4.2). Participants lay flat on their backs and were asked to keep as still as possible in the MRI scanner. Ear plugs and ear defenders were provided to protect them from the scanner noise. Foam pads were placed either side of the subject’s head to restrict head movement. The duration of the scan was approximately 6 minutes.
Table 5.1
Clinical characteristics of the patient sample in the DTI study

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<th>Age at assessment, Y:M</th>
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5.2.4 Imaging data pre-processing

The data were received from the scanner in DICOM format and converted to ANALYZE format, which is suitable for analysis with the FSL software (Smith et al., 2004, Jenkinson et al., 2012) available at www.fmrib.ox.ac.uk/fsl. Visual inspection of raw diffusion scans was performed in order to identify corrupted data. One patient dataset was removed due to the evident signal loss, and one healthy volunteer dataset was removed as due to technical error the wrong protocol was applied.

Following this, the FSL brain extraction tool was used to strip the original b0 (no diffusion) images of non-brain tissues. Default fractional intensity threshold of .5 was applied as it has shown to produce good results consistently and without excessive or insufficient skull stripping (Smith, 2002). Before estimating the diffusion measures, the images were pre-aligned to each other in order to correct distortions caused by head motion and gradient coil eddy currents (Horsfield, 1999). The FSL Diffusion toolbox (Behrens et al., 2003) was used to estimate the diffusion tensors for each voxel using a simple least squares fit of the tensor model to the diffusion data (Smith et al., 2006). Following this, the tensor eigenvalues were calculated, which, in turn, permitted the calculation of the FA, MD, RD and AD, according to the formulae provided earlier, in section 5.1.2.

5.2.5 Tract-Based Spatial Statistics (TBSS)

Whole brain voxelwise statistical analysis of the FA, MD, RD and AD data was carried out using the TBSS tool of FSL (Smith, 2004). TBSS is a method of voxelwise DTI measures
analysis, devised by Smith et al. (2006). It uses non-linear registration and projection onto an alignment-invariant tract representation (the ‘mean skeleton’) in order to achieve robust and objective analysis of multi-subject DTI data, not compromised by unreliable registration algorithms or an arbitrary choice of spatial smoothing criteria (Figure 5.7).

Figure 5.7. Example of the mean FA skeleton overlaid on the mean FA image (A). The red lines (B) represent perpendicular directions to the local tract structure during the first stage of the ‘mean skeleton’ estimation. From (Smith et al., 2006).

Consistent with the TBSS processing pipeline, all of the subjects' FA data were aligned into a common space with the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a; Andersson, Jenkinson, & Smith, 2007b). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data were fed into voxelwise cross-subject statistics. The same obtained skeleton was also used for the MD, RD and AD analyses. TBSS uses the ‘most typical’ subject for the entire group as a registration target, in order to minimise the amount of
warping required for each subject. For the between-group analyses, an average image was derived from all of the participants in the study (patients and controls). For the patient regression analyses, a target was identified from the patient images only.

5.2.6 Regions of interest

Several regions of interest were defined for further analyses. The skeletonised FA mask was treated as the first ROI for investigation of the global change in the white matter microstructure in the PFT survivors compared to the controls (Figure 5.8). For the second ROI, a section of the arcuate fasciculus was manually traced on the FA skeleton bilaterally (Figure 5.9). Similarly, for the third ROI, a section of the superior cerebellar peduncle was manually traced on the mean skeleton (Figure 5.10). The MRI atlas of human white matter (Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005) was consulted for anatomical guidance while manually tracing the ROIs. The obtained ROI masks were then applied to the individual standardised FA, MD, RD and AD maps, and mean scalar values for all of the ROIs were extracted for each participant for further analyses.

Figure 5.8. Whole brain ROI mask based on the mean TBSS skeleton.
Figure 5.9. Left Arcuate Fasciculus (A) and Right Arcuate Fasciculus (B) ROI masks.

Figure 5.10. Left Superior Cerebellar Peduncle (A) and Right Superior Cerebellar Peduncle (B) ROI masks.
5.2.7 Data analyses

5.2.7.1 Voxel-wise analyses of the between – group differences in FA, MD, AD and RD

An independent sample t-test was used to investigate the voxel-wise differences in the DTI measures between the PFT patients and the healthy controls. To allow for a robust statistical inference, the Randomise FSL function (Winkler et al., 2014) was used, with the number of permutations set to 5000. Family-wise error was corrected for with the threshold of p<0.05 using the threshold-free cluster enhancement option (TFCE). The white matter tracts were identified using the ICBM-DTI-81 WM labels atlas (Mori et al., 2005). As a result of the inter-group voxel-wise comparisons, those voxels were identified where there were significant differences between the patients and controls in the FA, MD, RD and AD values. The design matrix for the between-group comparison is available in Appendix 19.

5.2.7.2 Comparative analysis of the ROIs-extracted DTI scalar values

The mean values of all of the DTI measures (FA, MD, RD and AD) were extracted from all of the regions of interest (whole brain, bilateral SCP and bilateral AF) for further comparison between the patients and the healthy controls. In addition, comparisons were made between the radiotherapy-treated and non-treated patients. A non-parametric Mann-Whitney U-test was applied in all cases, as it is not sensitive to the parametric test assumptions, which are likely to be violated in a small sample.
5.2.7.3 Relationship between the DTI scalars and language performance

Correlational analyses were performed to assess the relationship between the FA, MD, RD and AD values within the selected regions of interest and the measures of language performance: the CELF-5 Language Content Index (a measure of semantic access) and the Expressive Language Index scores (a measure of language production).

To further investigate whether white matter integrity predicts overt language performance in patients, regression modelling was performed on the whole-brain DTI data. A simple linear regression procedure was performed for each DTI metric (FA, MD, AD or RD), with Language Content and the Expressive Language index included in the model as covariates (eight regression procedures in total) (see Appendices 20 and 21 for design matrices). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 22, Chicago, Il, USA).

5.2.7.4 Standard space and anatomical atlases

A widely used MNI52 coordinate system was used for convenience and consistency with the fMRI study. For localisation of the WM structures, the current study used atlases available as part of the FSL package. Two atlases were used for the description of the WM structures. The ICBM-DTI-81 WM labels atlas defines 48 white matter tracts. The labels were created by hand segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects; mean age 39 years. In the JHU white-matter tractography atlas, 20 structures were identified probabilistically by averaging the
The results of running deterministic tractography on 28 normal subjects (Mori, 2005; Wakana et al., 2007; Hua et al., 2008). The ICBM-DTI-81 WM labels were preferred as these are the more detailed out of the two WM atlases. However, where no description was available, a second WM atlas was consulted. As no separate WM atlas of the cerebellum is available in the FSL package, the Probabilistic Cerebellar Atlas (Diedrichsen et al., 2009) was used for the cerebellar structures’ description, as in the previous fMRI study. This atlas was created by averaging the cerebellar lobule masks of the 20 individuals and aligned to the MNI space by both affine and non-linear registration approaches. Figure 5.11 provides a schematic illustration of the structures covered by the atlases.

![Figure 5.11](image)

*Figure 5.11. Schematic illustration of the atlases used for localisation of the WM structures. A. JHU DTI-based white matter atlas. B. Probabilistic cerebellar atlas. C. ICBM-DTI-81 atlas*
5.3 Results

5.3.1 Whole-brain analyses

5.3.1.1 Global changes in WM microstructure in PFT survivors

The whole-brain voxelwise analyses revealed one cluster where the FA index was significantly lower in the patients, one cluster where MD was significantly higher in the patients, one cluster where AD was significantly higher in the patients, and two clusters where RD was significantly higher in the patients. On visualisation, all clusters were very broadly distributed and each one was appeared as a large number of small clusters (Figures 5.12 – 5.16). Table 5.2 provides a summary of the cluster details.

Average FA, MD, AD and RD values were extracted from the skeleton-based whole brain ROI and compared between the groups, and a number of statistically significant differences were detected. The results of the comparisons for the patients and healthy controls are summarised in Table 5.3. The results for the comparisons between the radiotherapy-treated and non-treated patients are summarised in Table 5.4.
Table 5.2

Clusters of significant difference in DTI metrics between patients (P) and healthy controls (HC) in the whole-brain analysis

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$</th>
<th>Max Z-stat voxel</th>
<th>Other structures affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fractional anisotropy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; P</td>
<td>1</td>
<td>29037</td>
<td>.002</td>
<td>17</td>
<td>48% Right Cerebellum, Crus II, 8% Right Cerebellum, Crus I</td>
</tr>
<tr>
<td><strong>Mean diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P &gt; HC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Axial diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P &gt; HC</td>
<td>1</td>
<td>17332</td>
<td>&lt;.001</td>
<td>10</td>
<td>53% Right cerebellum, lobule IX, 41% Right Cerebellum lobule VIIIb</td>
</tr>
<tr>
<td><strong>Radial diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P &gt; HC</td>
<td>1</td>
<td>12345</td>
<td>&lt;.001</td>
<td>-15</td>
<td>81% Left cerebellum, lobule VIIIb, 11% Left cerebellum, lobule VIIIa, 5% Left Cerebellum, Crus II</td>
</tr>
<tr>
<td>2</td>
<td>2742</td>
<td>.024</td>
<td>-3</td>
<td>-22</td>
<td>Fornix</td>
</tr>
</tbody>
</table>

Figure 5.12. Fractional anisotropy (FA) contrast map (Controls > Patients). Red voxels mark regions of the skeleton where FA is significantly higher in the controls compared to the patients. There was no significant increase in FA on the opposite contrast (Patients > Controls). Grayscale images - MNI template brain. False colour images - thresholded statistical maps. The Z-coordinates refer to slice locations in MNI space.
Figure 5.13. Mean diffusivity (MD) contrast map (Patients > Controls). Red voxels mark regions of the skeleton where MD is significantly higher in the patients compared to the controls. There was no significant increase in MD on the opposite contrast (Controls > Patients). Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Figure 5.14. Axial diffusivity (AD) contrast map (Patients > Controls). Red voxels mark regions of the skeleton where AD is significantly higher in the patients compared to the controls. There was no significant increase in AD on the opposite contrast (Controls > Patients). Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Figure 5.15. Radial diffusivity (RD) contrast map (Patients > Controls). Red voxels mark regions of the skeleton where RD is significantly higher in the patients compared to the controls. There was no significant increase in RD on the opposite contrast (Controls > Patients). Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Figure 5.16. Areas of reduced FA and increased MD, AD and RD in patients, overlaid on the mean tract skeleton
### Table 5.3.
Comparison of the whole brain DTI metrics in the patients and healthy controls

<table>
<thead>
<tr>
<th>DTI metric, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Axial</td>
</tr>
<tr>
<td><strong>Patients, n = 15</strong></td>
<td>.42 (.02)</td>
<td>.79 (.03)</td>
</tr>
<tr>
<td><strong>Healthy Controls, n = 19</strong></td>
<td>.43 (.01)</td>
<td>.75 (.01)</td>
</tr>
<tr>
<td><em><em>Test of significance</em>, p</em>*</td>
<td>.006**</td>
<td>.001**</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>2.51</td>
<td>3.83</td>
</tr>
<tr>
<td><strong>Effect size, r</strong></td>
<td>.43</td>
<td>.66</td>
</tr>
</tbody>
</table>

* Mann-Whitney U-tests, one-tailed
** Significant after familywise error correction
Effect size $r = Z/\sqrt{N}$

### Table 5.4.
Comparison of the whole brain DTI metrics in the radiotherapy-treated (RT) and non-treated (Non-RT) patients

<table>
<thead>
<tr>
<th>DTI metric, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Axial</td>
</tr>
<tr>
<td><strong>RT patients, n = 7</strong></td>
<td>.42 (.01)</td>
<td>.78 (.02)</td>
</tr>
<tr>
<td><strong>Non-RT patients, n = 8</strong></td>
<td>.41 (.02)</td>
<td>.79 (.03)</td>
</tr>
<tr>
<td><em><em>Test of significance</em>, p</em>*</td>
<td>.31</td>
<td>.20</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>.58</td>
<td>.93</td>
</tr>
<tr>
<td><strong>Effect size, r</strong></td>
<td>.10</td>
<td>.16</td>
</tr>
</tbody>
</table>

* Mann-Whitney U-tests, one-tailed
** Significant after familywise error correction
Effect size $r = Z/\sqrt{N}$
### 5.3.1.2 Relationship between the global DTI indices and language performance

The correlational analyses using Pearson’s $r$ demonstrated no statistically significant relationships between the global FA, MD, RD or AD and the CELF-5 indices of interest (Language Content Index and Expressive Language Index) (Figure 5.17). This suggests that, although the groups differed from each other significantly, the individual level global measures of the WM microstructure and language performance were not related.

### 5.3.2 Superior Cerebellar Peduncle (SCP)

#### 5.3.2.1 Between-group differences in DTI measures within the SCP

Average FA, MD, AD and RD values were extracted from the bilateral SCP in the patients and the controls. Significant between–group differences were observed in MD, AD and RD, but not FA, with increased diffusivity measures in the patient group. The results are summarised in Table 5.5.

Average FA, MD, AD and RD values were also compared between the sub-groups of patients that had received adjuvant radiotherapy and those who had not. FA was significantly higher in the radiotherapy-treated sub-group in the left SCP (Table 5.6).

#### 5.3.2.2 Relationship between the DTI indices in the bilateral SCP and language performance

Correlational analyses using Pearson’s $r$ revealed no statistically significant association between FA, MD, RD or AD and the CELF-5 indices (Figures 5.18 and 5.19).
Figure 5.17. Relationship between the whole brain DTI indices and Language Content/Expressive Language Index scores in the patients and controls.
Table 5.5.  
**DTI indices within the bilateral SCP in the patients and healthy controls**

<table>
<thead>
<tr>
<th>DTI metric, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Superior Cerebellar Peduncle</td>
<td>Mean</td>
</tr>
<tr>
<td>Patients, n = 15</td>
<td>.59 (.04)</td>
<td>.79 (0.05)</td>
</tr>
<tr>
<td>Healthy Controls, n = 19</td>
<td>.60 (.04)</td>
<td>.72 (0.03)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>.33</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>z</td>
<td>.47</td>
<td>4.11</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.08</td>
<td>.70</td>
</tr>
<tr>
<td>Right Superior Cerebellar Peduncle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n = 15</td>
<td>.59 (.04)</td>
<td>.80 (0.05)</td>
</tr>
<tr>
<td>Healthy Controls, n = 19</td>
<td>.60 (.04)</td>
<td>.72 (0.02)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>.26</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>z</td>
<td>.68</td>
<td>4.46</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.12</td>
<td>.76</td>
</tr>
</tbody>
</table>

*Mann-Whitney U-tests, one-tailed. ** Significant after familywise error correction. Effect size = Z/√N

Table 5.6.  
**DTI indices within the bilateral SCP in the radiotherapy-treated (RT) and non-treated patients (Non-RT)**

<table>
<thead>
<tr>
<th>DTI metric, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Superior Cerebellar Peduncle</td>
<td>Mean</td>
</tr>
<tr>
<td>RT patients, n = 7</td>
<td>.61 (.03)</td>
<td>.80 (0.05)</td>
</tr>
<tr>
<td>Non-RT patients, n = 8</td>
<td>.56 (.02)</td>
<td>.78 (0.06)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>.003**</td>
<td>.27</td>
</tr>
<tr>
<td>z</td>
<td>2.66</td>
<td>.94</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.46</td>
<td>.16</td>
</tr>
<tr>
<td>Right Superior Cerebellar Peduncle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT patients, n = 7</td>
<td>.60 (.04)</td>
<td>.81 (0.05)</td>
</tr>
<tr>
<td>Non-RT patients, n = 8</td>
<td>.57 (.03)</td>
<td>.79 (.06)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>.10</td>
<td>.27</td>
</tr>
<tr>
<td>z</td>
<td>1.39</td>
<td>.69</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.24</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Mann-Whitney U-tests, one-tailed. ** Significant after familywise error correction. Effect size = Z/√N
Figure 5.18. Relationship between the DTI indices within the Left/Right Superior Cerebellar Peduncle and Language Content Index scores
Figure 5.19. Relationship between the DTI indices within Left/Right Superior Cerebellar Peduncles and Expressive Language Index scores
5.3.3 Arcuate fasciculus (AF)

5.3.3.1 Between-group differences in DTI measures within the AF

Average FA, MD, AD and RD values were extracted from the bilateral AF in the patients and the controls. Significant between-group differences were observed in FA with the higher values in the control group, and a larger effect size in the left-hemispheric AF. No statistically significant differences in MD, AD or RD were observed, suggesting that the overall displacement of water molecules within the AF was comparable between the patients and the controls. The results are summarised in Table 5.7.

Average FA, MD, AD and RD values were also compared between the sub-groups of patients that had received adjuvant radiotherapy and those that had not, and no statistically significant results were observed (Table 5.8).

5.3.3.2 Relationship between the DTI indices in the bilateral AF and language performance

Correlational analyses using Pearson’s r revealed no significant relationships between FA, MD, RD or AD and the CELF-5 indices (Figures 5.20 and 5.21).
Table 5.7.
*DTI indices within the bilateral AD in patients and healthy controls*

<table>
<thead>
<tr>
<th>DTI metrics, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Axial</td>
</tr>
<tr>
<td>Left Arcuate Fasciculus</td>
<td>.34 (.01)</td>
<td>.74 (.03)</td>
</tr>
<tr>
<td>Healthy Controls, n = 19</td>
<td>.36 (.02)</td>
<td>.73 (.02)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>&lt;.001**</td>
<td>.27</td>
</tr>
<tr>
<td>z</td>
<td>3.38</td>
<td>.71</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.58</td>
<td>.12</td>
</tr>
</tbody>
</table>

Right Arcuate Fasciculus

| Patients, n = 15 | .33 (.02) | .75 (.02) | 1.02 (.03) | .71 (.03) |
| Healthy Controls, n = 19 | .34 (.02) | .74 (.01) | 1.02 (.02) | .70 (.02) |
| Test of significance*, p  | .01**     | .27      | .32         | .42       |
| z                       | 2.20      | .64      | .50         | .23       |
| Effect size, r          | .38       | .11      | .09         | .04       |

*Mann-Whitney U-tests, one-tailed.** Significant after familywise error correction Effect size = Z/√N

Table 5.8.
*DTI indices within the bilateral AD in radiotherapy-treated (RT) and non-treated patients (Non-RT)*

<table>
<thead>
<tr>
<th>DTI metrics, mean (SD)</th>
<th>Fractional Anisotropy</th>
<th>Diffusivity scalars, E-3 mm²/s</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Axial</td>
</tr>
<tr>
<td>Left Arcuate Fasciculus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT patients, n = 7</td>
<td>.34 (.01)</td>
<td>.74 (.03)</td>
</tr>
<tr>
<td>Non-RT patients, n = 8</td>
<td>.35 (.02)</td>
<td>.74 (.03)</td>
</tr>
<tr>
<td>Test of significance*, p</td>
<td>.14</td>
<td>.43</td>
</tr>
<tr>
<td>z</td>
<td>1.16</td>
<td>.23</td>
</tr>
<tr>
<td>Effect size, r</td>
<td>.20</td>
<td>.04</td>
</tr>
</tbody>
</table>

Right Arcuate Fasciculus

| RT patients, n = 7     | .33 (.02)             | .75 (.02)                    | 1.02 (.03)                  | .70 (.02)                  |
| Non-RT patients, n = 8 | .33 (.02)             | .75 (.02)                    | 1.02 (.03)                  | .71 (.05)                  |
| Test of significance*, p  | .48                   | .39                          | .48                         | .20                        |
| z                       | .12                   | .35                          | .12                         | .93                        |

*Mann-Whitney U-tests, one-tailed.** Significant after familywise error correction. Effect size = Z/√N
Figure 5.20. Relationship between the DTI indices within the Left/Right Arcuate Fasciculi and Language Content Index score
Figure 5.21. Relationship between the DTI indices within the Left/Right Arcuate Fasciculi and Expressive Language Index score
5.3.4 Relationship between the WM integrity and language processing in patients: linear regression

The analysis revealed a prominent left-hemispheric cluster of 2044 voxels (16352 mm$^3$) where there was a significant positive relationship between the FA index and Language Content Index. Four small clusters of between 4 and 76 voxels (32 mm$^3$ to 608 mm$^3$) were detected in close proximity to the largest cluster. There were no other significant results for the Expressive Language Index and remaining DTI metrics. Details of the clusters are presented in Table 5.9 and shown in Figures 5.22 and 5.23.

Table 5.9
Predictive value of the DTI measures on language performance in the PFT patients

<table>
<thead>
<tr>
<th>DTI metric</th>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$</th>
<th>Maximum intensity voxel location (MNI space)</th>
<th>Other structures affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>1</td>
<td>2044</td>
<td>.022</td>
<td>x(-20), y(-14), z(-4)</td>
<td>Left Posterior limb of internal capsule/Cortico-spinal tract</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>76</td>
<td>.046</td>
<td>x(-29), y(-11), z(-16)</td>
<td>Left superior longitudinal fasciculus</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>61</td>
<td>.047</td>
<td>x(-6), y(-24), z(-27)</td>
<td>Left cortico-spinal tract</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>.05</td>
<td>x(-52), y(-40), z(-1)</td>
<td>Left superior longitudinal fasciculus</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>.05</td>
<td>x(-8), y(-29), z(-33)</td>
<td>Left cortico-spinal tract</td>
</tr>
<tr>
<td>MD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
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<tr>
<td>RD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expressive Language Index

<table>
<thead>
<tr>
<th>DTI metric</th>
<th>Cluster index</th>
<th>N of voxels</th>
<th>$p^*$</th>
<th>Maximum intensity voxel location (MNI space)</th>
<th>Other structures affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td></td>
<td></td>
<td></td>
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<td>AD</td>
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<td>RD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td></td>
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Threshold-free cluster enhancement, corrected for familywise error. Coordinates in MNI space, anatomical locations according to JHU ICBM-DTI-81 White-Matter Labels and JHU White Matter Tractography Atlas.

FA – fractional anisotropy, MD – mean diffusivity, AD – axial diffusivity, RD – radial diffusivity
Figure 5.22. Outcomes of the voxelwise regression analyses. Red voxels mark areas of the skeleton where a higher FA corresponds to a higher LCI score. Grayscale images - MNI template brain. False colour images - thresholded statistical maps. Z-coordinates refer to slice locations in MNI space.
Figure 5.23 Voxel clusters in the left hemisphere where a significant positive relationship was detected between FA and Language Content Index in the patients (red); overlaid on the mean FA skeleton.

5.4 Discussion

5.4.1 Global deterioration of the white matter quality in PFT survivors

The present study investigated the hypothesis that PFT survivors will display global deterioration in their WM quality, compared to healthy controls. This hypothesis is supported by the present findings of a widespread reduction in FA, and the elevation of the MD and RD. FA is one of the most commonly used composite measures, and is sensitive to microstructural changes, such as axonal degeneration and demyelination (Huettel et al., 2004). In our study, the clusters of significantly reduced FA were distributed across the whole brain and included locations such as the corpus callosum, the fornix, the right posterior thalamic radiation, the bilateral retrolenticular part of the internal capsule, the bilateral external capsule, the bilateral superior and anterior corona radiata, the bilateral longitudinal fasciculus, the bilateral fronto-occipital fasciculus, and the cerebellum. This finding is
relevant, as in the past studies of healthy subjects have demonstrated that a whole-brain reduction in the FA coefficient is associated with reduced cognitive control (Chaddock-Heyman, et al., 2013), a lower IQ (Schmithorst, Wilke, Dardzinski, & Holland, 2005), and poorer reading skills (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999).

Our findings are in agreement with other studies of the PFT population that have also reported a significant reduction in the FA coefficient globally. For example, Palmer et al. (2012) examined the microstructural WM changes in a sample of 40 medulloblastoma survivors and 40 healthy controls. Using the TBSS method, they also found that throughout the majority of the fiber tracts, the FA in the patient group was significantly lower compared to the control group. Similarly, Ruekriegel et al. (2015) investigated the relationship between the global skeletonised tract FA and performance on cognitive and motor function in 18 medulloblastoma and 14 pilocytic astrocytoma survivors. They reported that the global skeletonised FA correlated significantly with the IQ score, once again highlighting that the cognitive decline in the PFT population may be underpinned by a global deterioration of the WM quality.

Analysis of the diffusivity scalars (MD and RD) also revealed significant adverse global changes in PFT patients within the cerebellum, the fornix, the bilateral anterior thalamic radiation, the left cerebral peduncle, the bilateral superior cerebellar peduncle, the brainstem and the bilateral cortico-spinal tract. The abnormal increase in diffusivity along all tensor dimensions was particularly notable within the
cerebellum, indicating the lack of healthy myelin tissue. Often, a pathological increase in MD takes place alongside a reduction in FA (Assaf & Pasternak, 2008). In addition, fluid-filled structural cavities that remain following a tumour resection are most likely to have contributed to the observed effect, as CSF has a higher diffusivity compared to the WM tissue.

Despite expected reduction of AD, this scalar was actually increased in PFT survivors compared to controls. There is much less consistency in the literature regarding the effects of pathological changes on AD. As mentioned previously, experimental animal models of multiple sclerosis suggest decrease of AD as a function of axonal degeneration (Budde et al., 2009). At the same time, in the studies of other neurodegenerative conditions, including Huntington’s and Alzheimer’s disease AD was reported to be increased (e.g., Acosta-Cabronero, Williams, Pengas, & Nestor, 2009; Rosas et al., 2010). In a recent study of 34 long-term survivors of medulloblastoma, no differences in AD was found across any of the brain regions, when compared to healthy controls (Moxon-Emre et al., 2016). Thus, it is difficult to make firm inferences, based on the AD changes alone. Yet, reduced anisotropy and elevated MD and RD suggest widespread microstructural deterioration of the WM tracts in our patient sample.

**5.4.2 Suggested mechanisms behind the supratentorial changes in the WM in PFT survivors**

Supratentorial regions are located distally in relation to the primary injury site in PFT patients. For this reason, the
mechanisms leading to the changes in the DTI scalars are not immediately obvious, and several factors may be at play. Adjuvant radiotherapy is perhaps the most commonly implicated factor that has been linked to the deterioration of the distal WM quality in PFT survivors (e.g., Mabbott et al., 2006; Rueckriegel et al., 2010; Law et al., 2011; Palmer et al.; 2012; Moxon-Emre et al., 2016). Section 5.4.6 provides more detailed account of the suggested influence of irradiation on the neural tissue, as well as discussion of the present results in light of existing evidence.

Other mechanisms potentially contributing to the distal microstructural changes in DTI metrics could be related to the neurotoxic effects of the hydrocephalus and adjuvant chemotherapy treatment. Rueckriegel et al. (2010), with a sample of 30 PFT patients, demonstrated reduced FA in the supra-tentorial areas in both medulloblastoma and pilocytic astrocytoma patients. For the astrocytoma group, who had not received any adjuvant treatment, the authors suggested that such a change may be due to the hydrocephalus, which leads to increased intracranial pressure and restricts diffusion. This in turn causes oedema of the periventricular brain tissue and potentially long-term damage to the white matter.

Equally, chemotherapy treatment has been associated with neurotoxic effects on the white matter with long-lasting consequences (Dietrich, 2010). It is difficult to disentangle the effects of radiotherapy and chemotherapy as often the two treatment modalities are used in combination in PFT patients. However, previous studies of other cancers, in particular leukaemia, have suggested a link between the neurotoxic effects of chemotherapy and treatment-induced
multi-focal disease of the white matter (Lai et al., 2004; Yagmurlu et al., 2008).

Finally, the phenomenon of diachisis has been cited as a probable cause of the adverse changes in the supra-tentorial white matter. It refers to a reduction in function in part of the brain after the disruption of an afferent pathway in a remote brain area (Meyer, Obara, & Muramatsu, 1993). Crossed cerebro-cerebellar diachisis (CCCD) refers to this effect specifically when connections between the cerebrum and the cerebellum are involved, and could account for the structural and functional changes in the supra-tentorial areas following an injury to the posterior fossa (Poretti & Boltshouser, 2012). Although CCCD has been named previously as the potential mechanism behind posterior fossa syndrome and cerebellar mutism (Miller et al., 2010; Law et al., 2012), it has not been widely discussed as the cause of the change in the diffusion parameters of the white matter in the supra-tentorial regions following PFTs. Studies of supra-tentorial tumours and stroke lesions have implicated CCCD in the progressive deterioration of the cerebellar white matter (e.g., Patay et al., 2014, Strother et al., 2016). It is, therefore, plausible to suggest that the reverse may be true when explaining the white matter deterioration in the supratentorial regions, following white matter damage at the cerebellar level. It is most likely, however, that CCCD, and the effects of the adjuvant treatment in combination contribute to the structural degeneration of the supra-tentorial WM in PFT patients.
5.4.3 Elevated diffusivity within the SCP section of the dentate-thalamo-cortical tract

The superior cerebellar peduncle (SCP) was investigated as it is a white matter structure that forms part of the DTC tract. It is particularly at risk of being damaged by tumour invasion or surgical resection in PFT patients. Previously, a number of studies using diffusion-weighted techniques have focused on the assessment of the white matter microstructure at the cerebellar peduncle level, where adverse changes have been found in patients who subsequently developed posterior fossa syndrome and/or mutism (Morris et al., 2009; Ojemann et al., 2013, McEvoy et al., 2016).

We did not find a statistically significant difference in the FA within the bilateral SCP between the patients and the controls. However, as hypothesised, MD and RD scalars were significantly elevated in the patients. This suggests that, although the overall directionality of diffusion was not affected, displacement of the water molecules in this region was abnormally large along all of the tensor eigenvectors. Similar to our findings, Oh et al. (2016) did not observe group differences in FA within the cerebro-cerebellar pathways between PFT in 19 pilocytic astrocytoma patients, 9 medulloblastoma patients and 20 healthy controls. Yet, the authors reported a reduced volume of the DTC tract in medulloblastoma survivors, in particular those who had developed cerebellar mutism post-surgery, by applying the tractography method to the efferent and afferent projections within the cerebro-cerebellar white matter circuitry. It may be possible, therefore, that WM degeneration in this region leads to both volume loss
and elevated diffusivity. As mentioned previously, MD is frequently used as a measure of WM maturation, and it typically decreases with age (Snook, Plewes, & Beaulieu, 2006). It would therefore be potentially interesting to investigate in future studies whether the tumour and its treatment has adverse effects on the superior cerebellar peduncle maturation, which would result in a reduced volume and increased MD, consistent with our observations.

Once again, contrary to the initial hypothesis, AD was also elevated in the bilateral SCP in patients compared to controls. Similarly to the the global AD changes, discussed earlier, evidence in relation to the change in this metric specifically within the cerebello-cerebral circuitry is also mixed. For example, Law et al. (2011) reported that older age at diagnosis was associated with lower AD for the left-originating cerebello-thalamo-cortical tract, but larger tumour size was associated with higher AD for the right portion of the same tract. McEvoy et al. (2016) reported AD reduction within the right SCP in patients with the history of posterior fossa syndrome. Studies of Friedrich’s ataxia where increase of AD within the SCP has also been observed, have attempted to provide explanation to the pathophysiology of this phenomenon. It has been suggested that AD increase reflects severity of the damage to the dentate nuclei, specifically the pre-synaptic portion of the dentate-thalamo-cortical pathway, a so-called ‘dying-back phenomenon’ (Pagani et al., 2010; Nave et al., 2011). This explanation could also be applicable to PFT patients, as dentate nucleus is frequently damaged by the tumour and the surgery.
5.4.4 Adverse changes in WM integrity within the arcuate fasciculus

The arcuate fasciculus was investigated as it is the pathway that is thought to support communication between the cortical language-processing centres, namely Broca’s area and Wernike’s area. Classical disconnectionist theory (Catani & ffytche, 2005) postulates that disruption to the WM connection will lead to deficits in overt functions, facilitated by this pathway, in our case the language function. Indeed, the relationship between the reduced FA index within the arcuate fasciculus and disorders of language has been reported before in patients with other medical conditions (Andrade et al., 2015, Ivanova et al., 2016) and supratentorial tumours (Kinoshita et al., 2014).

As hypothesised, the present study found significant inter-group differences in the FA coefficient within the bilateral arcuate fasciculi. The patients, as a group, had a significantly lower FA in both the left and right arcuate fasciculi in comparison to the controls. The observed effect was large in both the left and right arcuate fasciculi but more pronounced in the left hemisphere. The previously discussed phenomenon of the CCCD may underlie the microstructural changes in the arcuate fasciculi subsequent to cerebellar damage, as the cerebellum is connected to distributed regions of the cerebral cortex, involved in language processing (Schmahmann et al., 1997; Booth et al., 2007; Marien et al., 2014).

Although a reduced FA was observed in the arcuate fasciculi of the PFT group, who also under-performed on the overt language measures, a direct causal relationship could not
immediately be assumed, as other mediating factors could be involved. The relationship between overt language performance and global and local changes in WM were examined separately in more detail, and are discussed in the next section.

5.4.5 WM microstructural integrity and overt language performance

5.4.5.1 Correlational analyses

The relationship between WM integrity and language performance was investigated in two ways. First of all, correlational analyses were performed between the DTI scalar values, extracted from the ROIs, and the CELF-5 indices. Secondly, regression analysis was performed to locate regions where WM integrity predicts language performance in the patient group.

The first approach, using the global tract skeleton, superior cerebellar peduncle and arcuate fasciculus masks as the ROIs, did not yield statistically significant results. In relation to the whole-brain analysis, this may indicate that evaluation of the global state of WM may be useful for general between-group comparison, but not specific enough to be related to any particular function. Indeed, the WM tracts differ substantially in their functional specialisation (Catani & de Schotten, 2012), and warrant more detailed, localised analysis, when specific linguistic abilities are being investigated.

Less expectedly, there was no relationship between any of the DTI scalar values extracted from the SCP and CELF-5 indices. In a number of PFT population studies, SCP WM decline has been associated with the occurrence of posterior fossa
syndrome and post-operative mutism (Ojemann et al., 2013; Avula et al., 2015; McEvoy et al., 2016). It must be acknowledged, however, that post-operative absence of speech is not the same as loss of language (although McEvoy et al. (2016) uses these terms interchangeably). Therefore, our negative findings are not comparable with these reports.

To the best of our knowledge, the only other study that has demonstrated the link between aspects of language processing beyond speech production and white matter integrity within the superior cerebellar peduncle is that by Travis et al. (2015). The authors investigated cerebellar white matter pathways and reading skills in term-born (n = 26) and pre-term (n = 19) children, and found an association between the FA in the right superior cerebellar peduncle with reading comprehension and phonological decoding, showing this structure’s involvement in reading processes. Surprisingly, however, the correlation was negative, with lower FA values corresponding to improved reading scores. Clearly, evidence of the SCP role in language processing in the PFT group is still lacking, and more research is needed to validate our negative findings.

Similarly, and contrary to the hypothesis, no relationship was detected between the DTI and CELF-5 indices in the bilateral AF, despite the tract being closely associated with modulation of the language function. This suggests that on the individual level, lower FA scores did not correspond to poorer performance in terms of language content and expression. Contrary to our findings, studies have previously postulated the role of the right arcuate fasciculus in the non-expressive aspects of language processing. For example, Horowitz-Kraus,
Wang, Plante, & Holland (2014) in a sample of 21 typically-developing adolescents, reported a positive association between the FA within the bilateral AF and reading comprehension skills. In another study, Loui, Li, & Schlaug et al. (2011) found a positive relationship between the FA in the right AF and pitch-related grammar learning skills in 16 healthy volunteers. Gullick & Booth (2015), in a longitudinal study of 30 children, reported an association between a decreased FA and a progressive decline in reading skills.

In trying to explain our negative findings, it is possible that the ROI mask did not encompass sections of the tract that may be involved in the modulation of the linguistic functions assessed by the chosen CELF-5 indices (Language Content and Expressive Language). After all, the anatomy of the arcuate fasciculus is a lot more complex, comprised of several segments (Catani & Jones, 2005), (Figure 5.6), and could only be reconstructed in its entire complexity using a tractography method. Another possibility is that, if the effect was subtle, our study with the present sample size was simply not powerful enough to detect it. In any case, this is the first reported investigation of the structural integrity of the AF in PFT patients, and our findings provide a useful starting point for future investigations.

**5.4.5.2 Regression analyses**

The regression analysis approach proved to be more successful in determining the relationship between white matter integrity and overt language performance. In the patients, a significant association was detected between the CELF-5 Language Content Index and the FA values within the
left-hemispheric posterior limb of the internal capsule, the cortico-spinal tract, the corona radiata and the anterior thalamic radiation. Previously, deterioration of these structures in PFT patients has been associated with motor and processing speed deficits. For example, Lui et al. (2007), in a sample of 30 PFT patients, observed an association between a reduced FA within the cortico-spinal tract and contralateral motor weaknesses. Palmer et al. (2012), in a study of 40 long-term medulloblastoma survivors, reported an association between FA values and processing speed in a range of regions, including the corona radiata and the internal capsule. For the first time, we are able to demonstrate the relevance of these projection fibers to aspects of language processing, not reliant on motor control, including the understanding of concepts and categories, the comprehension of associations and relationships among words, and interpretation of factual and inferential information.

**5.4.6 Effects of radiotherapy on global and local WM microstructural integrity**

The present study also investigated the differences in the WM microstructure between the patients treated with radiotherapy and those who had not received radiotherapy as part of their tumour treatment. Contrary to the hypothesis, there were no significant differences in the majority of the global and local DTI measures. The only statistically significant difference in the FA coefficient was observed within the left SCP. However, the direction of this difference was the opposite of what was expected, with the radiotherapy-treated patients showing a higher FA value, compared to the rest of the patient sample.
The pathophysiology of radiation-induced white matter damage is complex and still not completely understood. Animal models have shown that the extent of the damage and subsequent cognitive decline is associated with the dose of radiation and the time that has elapsed since treatment; higher doses and a longer timeframe being associated with more significant cognitive decline (e.g., Yoneoka et al., 1999). Focal cerebral radionecrosis, which mainly affects the white matter, is a delayed complication of radiotherapy. Typically, it is accompanied by vascular lesions that contribute to the breakdown of the blood-brain barrier, and vasogenic oedema, remote from the site of primary irradiation (Tsuruda et al., 1987; Sundgren & Cao, 2009). In addition, radiation-induced white matter damage includes myelin and axonal loss, fibrotic thickening of the small blood vessels in the deep WM, intracellular oedema and WM gliosis (Soussain et al., 2009).

WM deterioration, associated with cranial irradiation, has been reported in PFT patients, both in the form of a reduction in the WM volume (Mulhern et al., 1999; Riggs et al., 2014), and as an adverse change in the diffusion-derived metrics (Mabbott et al., 2006; Rueckrigel et al., 2010; Law et al., 2011; Palmer et al.; 2012). In a recent study by Moxon-Emre et al. (2016), the authors reported a global decrease in fractional anisotropy in PFT patients who had received a standard or increased dose of radiation \((n=17)\), but not in those who had received a reduced dose of radiation \((n=17)\). This suggests that, while any amount of adjuvant radiotherapy increases the risk of WM damage, the extent of this damage is highly variable, depending on the dose received. In the present study, there were only seven patients who had received radiotherapy as
part of their treatment. With such a small sample, and due to some missing clinical information, stratification by radiation dose was not possible. Thus, the findings from the radiotherapy and non-radiotherapy sub-group comparisons should not be considered conclusive.

5.4.7 Limitations of the study

The limitations of the current study must be acknowledged for a more objective appraisal of its results. Firstly, the TBSS method does not allow for reliable evaluation of the peripheral segments of the WM tracts, which often vary between individuals, and are excluded from the analyses. For this reason, the TBSS findings are better viewed as an initial step in identifying the major differences across the groups, which is subsequently followed up by more precise methods (Feldman et al., 2010). In addition, when investigating specific WM pathways, such as the DCT tract or the Arcuate Fasciculus, fiber tract reconstruction may be a more informative method that takes into account patients’ individual variability. Tractography allows comparison of the fiber connections across individuals, even if the precise location of the tract varies (Feldman et al., 2010).

In addition, the small heterogeneous sample of the present study may have obscured subtle effects such as that of the radiotherapy treatment. For the same reason, the influence of other potentially important aspects, such as age at diagnosis, radiotherapy dose and recovery time, on the WM microstructural integrity was not possible to factor into the analysis. Ideally, future investigations of the WM in the context of language deficits should be carried out with larger,
more homogenous cohorts of patients in order to address these limitations.

5.4.8 Conclusions

The present study reported an investigation of the WM microstructure in PFT survivors, in relation to the observed overt language deficits. For the first time, it was possible to identify several prominent left-hemispheric clusters, where FA was significantly associated with overt language performance in PFT survivors, involving the posterior limb of the internal capsule, the cortico-spinal tract, the corona radiata and the anterior thalamic radiation.

Our findings also add to the growing body of literature reporting widespread deterioration of the white matter microstructure in long-term PFT survivors. In the study's patient sample, adverse changes in key DTI metrics were detected both proximal and distal to the primary injury sites, in a range of regions, including the cerebellum, the corpus callosum, the fornix, the right posterior thalamic radiation, the bilateral anterior thalamic radiation, the bilateral retrolenticular part of the internal capsule, the bilateral external capsule, the bilateral superior and anterior corona radiata, the bilateral longitudinal fasciculus, the bilateral fronto-occipital fasciculus, the left cerebral peduncle, the bilateral superior cerebellar peduncle, the brainstem and the bilateral cortico-spinal tract.

Locally, anisotropy was reduced in patients in the bilateral arcuate fasciculi, while diffusivity metrics were elevated in the bilateral superior cerebellar peduncles. The FA, MD, AD and RD values were comparable between the radiotherapy and
non-radiotherapy sub-groups of patients, with the exception of the left SCP, where FA was significantly higher in the radiotherapy-treated patients. These findings once again highlight the risk of widespread long-term WM damage in PFT survivors, and offer a new insight into the specific structures that are crucial for the preservation of linguistic abilities.
Chapter 6: Clinical features and functional outcomes: a patient-focused investigation

Key findings

- Exploratory cluster analysis is performed in order to identify naturally emerging groups of PFT cases, based on language outcomes and clinical features;
- Younger age at diagnosis is associated with diminished language skills in radiotherapy-treated patients, but not in those who did not receive adjuvant radiotherapy;
- 38% of the PFT survivors met the criteria for a diagnosable language disorder (LD), in either the expressive or receptive, or both domains;
- Patients with signs of a language disorder also showed significantly poorer oro-motor reflex control and intelligibility of speech, compared to patients without signs of a language disorder;
- Among three patients with a history of cerebellar mutism, the poorest language outcomes (but not cognitive outcomes) were observed in the patient with the longest duration of mutism;
- There was no difference in the amount of the above-threshold activation during fMRI task between LD and non-LD patients;
- On DTI, LD patients have demonstrated reduced FA index compared to non-LD patients within the left arcuate fasciculus.

6.1 Introduction

The present patient-focused investigation is comprised of two parts. In Part 1, a cluster analysis method is applied
to investigate the relationship between the clinical history factors and language outcomes in PFT survivors. To the best of our knowledge, this approach has not been previously used in the neuropsychological studies of the PFT population. Unlike linear modelling approaches such as regression that quantify the predictive value of the clinical factors on a given outcome, cluster analysis can offer insight into what features are shared between patients who present with similar outcomes at the time of assessment (Everitt, Landau, Leese, & Stahl, 2011). This is particularly useful in retrospective studies with small samples where controlled manipulation of the predictor variables is not possible.

Part 2 investigates the relationship between patients’ oro-motor functioning and language processing abilities. Dysarthria evaluation is a core part of the functional assessment following a brain injury of any aetiology, predominantly with the aim of establishing a safe feeding routine. In this study, we will investigate whether patients displaying overt signs of a language processing disorder, also demonstrate signs of poor oro-motor control. CELF-5 assessment will be used as a benchmark to differentiate the patients displaying clinically significant or sub-clinical signs of aphasia from those who do not display such signs. Oro-motor functioning will then be compared between these two sub-groups. Although aphasia and dysarthria are two distinct aspects of communication disorders, their frequent co-occurrence mean that there is a scope for exploring the relationship between the two in PFT survivors more deeply (McDonald, Code, & Togher, 2016).
In addition, this section will investigate how a history of cerebellar mutism, as an acute speech disorder, relates to the language functioning in a long-term recovery phase. Finally, this section is also concerned with the investigation of the neuroimaging markers of the observed language deficits in PFT survivors, previously not reported in the literature. Cortical activation during the fMRI task, described in Chapter 4 of the present thesis will be compared between sub-groups of PFT patients with and without the signs of a language disorder. DTI anisotropy and diffusivity scalars, reported in Chapter 5, will be compared between these sub-groups of patients in order to advance current limited understanding of the neural correlates of the language processing deficits in long-term PFT survivors.

6.1.1 Aims and objectives

The present investigation was carried out with the overall objective of improving our understanding of how patients’ clinical history factors, overt oro-motor abilities and neuroimaging markers relate to their long-term language outcomes.

Several aims were pursued:

- To assess the effectiveness of a cluster analysis method for analyzing relationships between clinical predictors and functional outcomes;

- To assess the degree of clinical significance of the observed language deficits in a patient group in order to evaluate whether the prevalence of language impairments
is higher in the PFT survivors compared to the general population;

- To investigate if oro-motor abilities relate to high-order language processing in PTF survivors, and whether routine dysarthria assessment can be used as a language disorder screening measure;

- To analyse language outcomes in a sub-group of PFT patients with the history of a transient cerebellar mutism in order to improve current limited understanding of the long-term prognosis for this specific group of patients;

- To describe functional and diffusion MRI neural markers of a language disorder in PFT survivors.

6.2. **Part 1: Forecasting functional outcomes using clinical predictor variables**

6.2.1 **Background**

One challenge in regard to investigating functional outcomes in PFT patients has always been the high heterogeneity in patients’ clinical histories and, as a consequence, the large number of extraneous variables that cannot be reliably controlled for in small-scale studies. Tumours vary greatly in terms of their histological presentation and location, leading to a variety of treatment strategies. In addition, children are at different developmental stages at the time of diagnosis and have varying durations of symptoms before the commencement of treatment. Some have additional complications such as hydrocephalus, ataxia or posterior fossa syndrome. Finally, children's socio-economic circumstances vary
greatly, which leads to differences in terms of their access
to rehabilitation and educational support, depending on
the availability of the services in the area where they grow
up. With the incidence of PFTs currently being at around
300 cases per year in the UK (The Brain Tumour Charity,
2016), it is clear that initiating large scale studies in which
the participants’ characteristics are homogenous enough
to achieve reliable forecasting of the outcomes is a
complicated endeavour.

‘Outcomes’ in itself is a multi-faceted notion, which can
mean different things, depending on the professional
specialisation of the researchers and the aim of the study.
Oncological and neurosurgical studies typically discuss
outcomes in terms of duration of survival and post-
treatment complications, while the psychological literature
predominantly focuses on subsequent cognitive
functioning, psychosocial adaptation and quality of life.
Nevertheless, there appears to be an overlap in the
predictor variables discussed in the clinical and
psychological literature. Frequently mentioned factors
include tumour histology and treatment, surgery-related
and temporal factors, and perioperative complications,
discussed in more details in the subsequent sections.

6.2.1.1 Histology and treatment-related
factors

Although tumour and treatment types are often discussed
as separate risk factors, it is logical to consider them in
combination as tumour histology is the major determining
factor in the choice of treatment regimen. Malignant
neoplasms such as medulloblastoma are typically treated with a combination of surgery, radiotherapy and chemotherapy. In contrast, benign astrocytomas typically require surgery and sometimes adjuvant chemotherapy, with radiotherapy only being used in cases of relapse or progression (Bonfield & Steinbok, 2015). Finally, diffuse intrinsic pontine gliomas (DIPG) are not suitable for surgical resection and are treated with radiotherapy and chemotherapy (Lin & Prados, 2016). Only 10% of paediatric DIPG patients survive for longer than 2 years (The Brain Tumour Charity, 2017) meaning that their long-term functional outcomes are rarely discussed in the literature.

Radiotherapy is the factor that is most frequently cited as a causal factor in regard to poor long-term functional outcomes. Hence, medulloblastoma radiotherapy-treated patients tend to have the worst long-term prognosis in terms of cognitive, linguistic, psychological and motor functioning (e.g., Copeland, deMoor, Moore, & Ater, 1999; Mabbott et al., 2006; Aarsen et al., 2009; Rueckriegel et al., 2009, Piscione et al., 2014; Hanzlik, Woodrome, Abdel-Baki, Geller, & Elbabaa; 2015). For this reason, current PFS treatment protocols do not recommend cranial radiotherapy in children under the age of three, in order to prevent a severe future impact on intellectual functioning.

Recently, the literature has focused on radiotherapy dose as a potentially mediating factor, with lower doses being associated with better outcomes. For example, Moxon-Emre et al. (2014), in a review of 113 PFT cases, found
that, out of all radiotherapy protocols, reduced dose irradiation with subsequent tumour bed boost was associated with stable intellectual development trajectories. Conversely, those patients that received higher initial and boost doses demonstrated an intellectual decline in the long-term recovery period. However, Robinson et al. (2013), in a meta-analysis of 38 studies published between 1983 and 2011, concluded that significant cognitive deficits were evident regardless of whether the RT dose was standard or reduced. This suggests other factors in addition to radiotherapy dose contribute towards the long-term cognitive outcomes.

Astrocytoma outcomes tend to be a lot more favourable, largely due to the absence of radiotherapy, with many studies reporting close-to-normal outcomes in terms of cognition, quality of life and physical functioning (e.g., Richter et al., 2005; Rasalkar et al., 2013). Some studies, however, urge that astrocytoma diagnosis does not automatically mean problem-free recovery, and these patients can still face an increased risk of developing long-term functional deficiencies. For example, Aarsen et al. (2004) and Aarsen et al. (2009) studied only astrocytoma survivors and reported below-the-norm scores on a range of neurocognitive tests, including visuo-spatial ability, recognition and recall, sustained attention, verbal intelligence, and naming. Other investigators also reported executive, adaptive, neurological and psychological deficits in non-radiotherapy treated AC survivors (Beeb at al., 2005; Vaquero et al., 2008; Turner et al., 2009).

Fewer studies have discussed the impact of chemotherapy
on the observed intellectual outcomes, largely due to the difficulty of disentangling chemotherapy effects from those induced by radiotherapy, as the two adjuvant treatments are often used in combination. In one such study Holmquist & Scott (2002) investigated the effects of various chemotherapy agents in 54 brain tumour patients, and reported that vincristine, cytoxan, cisplatin, and/or VP16 (etoposide) were related to poorer attention, social withdrawal, and signs of anxiety and depression, when compared to other chemotherapy agents, including carboplatin, BCNU (carmustine), idarubicin, topotecan and methotrexate. However, the authors have acknowledged that heterogeneity of the sample may have negatively impacted the study’s internal validity. More research is needed to reliably elucidate the effects of chemotherapy drugs on the neurocognitive sequelae.

### 6.2.1.2 Surgery-related factors

Almost all PFT tumours, with the exception of DIPG, are treated with some kind of surgical intervention (Lassaletta, Bouffet, Mabbott, & Kulkarni, 2015). Thus, the impact of surgery on long-term outcomes cannot be underestimated. Key surgery-related factors that have been implicated in the long-term prognosis are the extent of resection and the surgical approach. In the past, studies have reported better cognitive outcomes in patients where total or near-total resection of the tumour mass was achieved (e.g., Aarsen et al., 2009). In an RCT involving 203 patients, Albright et al. (1996) reported that a residual tumour volume of less than 1.5 cm$^3$ in children over 3 years of age was associated with improved 5-years progression-free
survival. However, in a recent study involving 787 MB patients, Thompson et al. (2016) concluded that the positive effect of the maximal extent of resection is attenuated when molecular sub-type is considered, and in cases of small residual tumour portion irradiation may prove more beneficial than gross total resection.

Surgical approach has been discussed in the literature as a potential factor in the development of post-surgery complications. For example, tumours of the fourth ventricle are typically surgically managed using a trans-vermian approach, which involves a posterior median craniotomy/craniectomy and splitting of the vermis. It has been observed that vermian damage is predictive of the long-term neuropsychological and neurological deficits (Puget et al., 2009). An alternative, trans-cerebello-medullary fissure (or telovelar) approach enables sparing of the vermis, and is thought to lead to more favourable outcomes (Shimoji et al., 2009, Qiu et al., 2016). This technique, however, is only beneficial for the patients with ependymomas of the 4th ventricle, but it is not always applicable to the cases where tumour is located in other structures of the posterior fossa.

### 6.2.1.3 Temporal factors

Age at diagnosis may play a significant role in observed long-term outcomes. For example, it has been observed that cerebellar lesions in adults lead to less pronounced functional deficits, compared to children (Timman & Daum, 2010). This has been explained by the pivotal role of the
cerebellum in the neurodevelopmental process. Wang, Kloth, & Badura (2014) proposed the term ‘developmental diaschisis’ to describe the mechanism whereby disruption of the developing cerebellum impacts the organisation and function of the distal, supra-tentorial structures. This implies that should the cerebellum be damaged early in childhood it will have secondary, downstream, effects on later cognitive development.

Studies of PFT paediatric patients demonstrate that a younger age at diagnosis impacts intellectual morbidity, and that craniospinal irradiation at a younger age may play a significant mediating role in this effect (e.g., Dennis et al., 1996; Copeland et al., 1999). A meta-analysis of 38 studies, published between 1983 and 2011 concluded that children diagnosed with PFT under the age of 7 were significantly more likely to exhibit long-lasting cognitive deficits than PFT patients diagnosed at an older age (Robinson et al., 2013).

6.2.1.4 Peri-operative factors

Pre-operative hydrocephalus is observed in up to 70%-90% of PFT patients (Le Fournier et al., 2017) and is considered to be an unfavourable factor (Lassaletta et al., 2015). It occurs when the tumour mass restricts the normal flow of CSF, leading to the accumulation of fluid, expansion of the ventricles and absolute increase in the periventricular water and sodium content (hydrocephalic, or interstitial oedema). The clinical manifestations of hydrocephalic oedema are psychomotor slowing and gait disorder (Merritt, 2010). When hydrocephalus is present,
surgical intervention is necessary in order to reduce the intracranial pressure. Approaches to hydrocephalus management include ventriculo-peritoneal shunt, endoscopic third ventriculostomy, and temporary ventricular drainage before or after tumour resection (Le Fournier et al., 2017).

A large proportion of children require permanent hydrocephalus treatment post-surgery, which has also been found to negatively affect their perceived quality of life in the long-term recovery phase (Kulkarni, Piscione, Shams, & Bouffet, 2013). Some of the reliable predictors of the need for such treatment include a younger age at diagnosis, pre-operative hydrocephalus, a higher tumour grade, radiotherapy and metastases (Odame et al., 2006; Riva-Cambrin et al., 2009; Lam, Reddy, & Jea, 2015). In terms of the long-term neurocognitive outcomes, influence of hydrocephalus in still not completely understood. Davis et al. (2011) in a sample of 15 PFT survivors observed substantial variation in the cognitive and motor test performance. Moderate hydrocephalus and shunting appeared to be associated with better outcomes, yet absence of hydrocephalus did not necessarily result in the absence of cognitive deficits.

Similarly, ataxia can be observed both pre- and post-treatment in PFT patients. Ataxia is defined as imbalance and incoordination which can arise due to a variety of different causes, including structural lesions of the cerebellum and brainstem, such as a tumour of the posterior fossa (Winchester, Singh, & Mikati, 2013).
Cerebellar sites that have been associated with ataxia include the fastigial and interposed nuclei, as well as the inferior vermis (Schoch, Hogan, Gizewski, Timmann, & Konczak, 2010; Piscione et al., 2014). Ataxia is frequently observed during the patient’s first presentation to a clinic prior to diagnosis and often persists for months after treatment (Fiorillo, Rinaldi, & Foggia, 2010; Turkel, Krieger, O’Neil, Jubran, & Tavaré, 2012). Although most severe in the acute period, ataxia is by far the most common neurological long-term impairment following PFT treatment, ranging from mild coordination difficulties to severe trunk and extremity control, which inadvertently impact patients’ quality of life (Pollack, 2012).

### 6.2.1.5 Posterior Fossa Syndrome (PFS) and Cerebellar Mutism Syndrome (CMS)

As briefly discussed in Chapters 2 and 3, cerebellar mutism syndrome (CMS) is a transient loss of speech that occurs in up to 30% of PFT patients, and lasts from several days to several months after surgery. CMS frequently occurs as part of Posterior Fossa Syndrome (PFS), which is characterised by a broad range of neurological, neuropsychological and speech/language symptoms, including personality changes, poor memory and attention, spontaneous uncontrolled movements, hypotonia, adynamic vocalisation and dysarthria (Gugrunardottir et al., 2016), (Figure 3.2). The underlying causes of CMS are still being explored, and there are ongoing attempts to build pre-operative risk stratification models that can reliably identify patients at risk of this complication.
(Dineen et al., 2015). In the largest prospective study of CMS to date, involving 450 children with medulloblastoma, it was linked to brainstem invasion (Robertson et al., 2006). In addition, a number of neuroimaging studies have attributed the pathology to disruption of the communication between the dentate nucleus of the cerebellum and the cerebrum in various locations along the dentate-thalamo-cortical (DCT) pathway (Law et al., 2012; Ojemann et al., 2013; Soelva et al., 2013).

Interestingly, in contrast to the presumed benefits of total tumour resection, Korah et al. (2010) reported that PFS occurred more frequently in patients who had experienced more aggressive surgery and had less of a residual tumor on MRI evaluation, possibly emphasising the significance of the mechanical damage to the DCT pathway.

Additional challenges in terms of dealing with acute symptoms of CMS/PFS, faced by both patients and their families, make post-operative management and rehabilitation of these patients particularly complex (Walker et al., 2014). Moreover, CMS and PFS have been linked to a range of problems that persist into the long-term recovery phase, including neurocognitive deficits (De Smet et al., 2009), withdrawal, depression and social problems (Brinkman et al., 2012; Lanier & Abrams, 2017), persistent dysarthria (Morgan et al., 2011; Tamburrini et al., 2015), and language deficits (Hudson et al., 1989; Hudson & Murdoch, 1992; Aarsen et al., 2004).
6.2.2 Method

6.2.2.1 Participants
The same cohort of patients as that described in Chapter 3 is referred to in the present study. The prevalence of the different tumour types was compared to the national statistics on paediatric posterior fossa tumours, provided by The Brain Tumour Charity (2016). In the present sample of 21, there were seven (33%) medulloblastoma patients, which is the same as the national incidence (33%), 11 (52%) pylocitic astrocytoma cases (compared to 35% of PFTs nationally), one patient (5%) with a high grade glioma (compared to 14% nationally), and two patients with a diagnosis of ependymoma (compared to 17% nationally).

In addition to the core information, referred to in the previous chapters, other relevant information was extracted from the patients’ records, including radiotherapy dose, chemotherapy drug, presence of pre-operative hydrocephalus, brainstem invasion and pre-operative ataxia.

6.2.2.2 Cluster analysis procedure
Understanding which clinical history factors contribute to the development of the functional outcomes in patients is important for long-term prognosis. Reliable predictive modelling such as multiple linear regression, however, is only possible when there is a sufficiently large sample size, with a common recommendation being at least 10 cases per predictor variable (Field, 2013). As mentioned
previously, PFT studies examining the relationships between the risk factors and functional outcomes are in the vast majority of cases suffer from the problem of the small sample sizes, undermining reliability of the the linear modelling-based conclusions and ultimately the power of the studies. In addition, because of the significant overlap between factors (for example, chemotherapy and radiotherapy) it is not possible to disentangle their effects in simple correlational analyses, and more sophisticated modeling of data may be required. One way of achieving this is multivariate classification of the variables into homogenous subsets prior to formal statistical analyses, such as the cluster analysis (Allen & Goldstein, 2014). Exploratory cluster analysis is often the procedure chosen to investigate how clinical cases relate to each other based on the features they share (Everitt, Landau, Leese, & Stahl, 2011). Clusters are defined in terms of internal cohesion (features of similarity between data points within a cluster) and external separation (features of difference between the data points belonging to different clusters), (Figure 6.1).

Figure 6.1. Examples of clusters with different internal cohesion and external separation. From (Everitt et al., 2011).
**Clustering variable selection procedure**

Cluster analysis assumes independence of the variables; thus the association between the continuous and categorical variables was tested prior to conducting the analyses. Recovery time correlated highly with age at diagnosis (Pearson’s $r = -0.92$, $p < 0.001$). Therefore, only one of these factors (Age at diagnosis) was included in the analyses, as it is discussed in the literature more extensively than recovery time. Age at diagnosis did not correlate with Core Language Score (Pearson’s $r = 0.25$, $p = 0.28$). Thus these two variables were assumed to be independent and suitable for further analyses.

Radiotherapy showed a high degree of association with tumour type (the Chi-squared test of independence gave the result $\chi^2(3) = 13.92$, $p = 0.003$). Thus these two variables could not be assumed to be independent. Radiotherapy was selected as the variable of interest because the representation of different tumour types in the sample was considerably uneven (e.g. eleven astrocytoma cases in comparison to only one high grade glioma case). Radiotherapy also had a high degree of association with chemotherapy ($\chi^2(1) = 10.83$, $p = 0.002$); thus the chemotherapy variable was also excluded as a variable from the main clustering process.

Since cluster analysis makes no distinction between dependent and independent variables, the outcome measures can also be used as cluster variables (Everitt et al., 2011). Key assessment outcome scores were considered as potential clustering variables, including the
CELF-5 Core the Language Score (CLS), the RPM score (a measure of non-verbal IQ), the PPB assembly score (a measure of manual dexterity) and the FDA-2 sum score (a measure of dysarthria). The variables were examined for significant correlations in order to satisfy the assumption of independence. Pearson’s correlation analyses demonstrated that CLS was correlated moderately with the RPM score ($r = .49, p = .03$) and the PPB score ($r = .42, p = .06$), and correlated highly with the FDA-2 sum score ($r = .6, p = .004$). Thus, only CLS was used as an additional clustering variable.

In summary, for the purpose of the cluster analysis in the present study, those clinical variables were selected for which reliable measurements were available for all patients with no missing data points in order to maximise the power of any significant findings. These included radiotherapy, age at diagnosis and recovery time. Those clinical and outcome measures that were not included as the main clustering variables, and where data was available for a sufficient number of participants, were included in the post-hoc descriptive evaluation of the clusters. These included tumour type, recovery time, tumour location, extent or resection, as well as the RPM, PPB and FDA-2 scores. Table 6.1 provides a summary of the cluster variable selection process.

**Clustering procedure selection**

A two-step cluster analysis procedure (Chiu et al., 2001) was performed using the Statistical Package for the Social Sciences software (SPSS version 22, Chicago, IL, USA). It was selected as, unlike traditional clustering techniques such as the hierarchical method, it offers the
Table 6.1
*Variables considered for inclusion in cluster analysis*

<table>
<thead>
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<th>Clinical history factors</th>
<th>Missing values</th>
<th>Moderate or high degree of association</th>
</tr>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Tumour type</td>
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<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>No</td>
<td>Tumour type / Radiotherapy</td>
</tr>
<tr>
<td>Tumour volume</td>
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<td></td>
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<tr>
<td>Tumour location</td>
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</tr>
<tr>
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<td>Chemotherapy</td>
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</tr>
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<tr>
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<td></td>
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<tr>
<td>Post-operative mutism</td>
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**Key assessment outcome variables**

<table>
<thead>
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<th>CLS (Core Language Score)</th>
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<th>CLS / RPM</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>PPB assembly score (manual dexterity)</td>
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<tr>
<td>FDA-2 sum score (dysarthria)</td>
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<td>CLS / FDA-2</td>
</tr>
</tbody>
</table>

**Final list of clustering variables, after removing variables with missing values and highly correlating variables**

- Age at diagnosis
- Radiotherapy
- CLS (Core Language Score)

**Additional cluster evaluation variables, used for description of the obtained clusters**

- Recovery time
- Tumour type
- Tumour location
- Extent of resection
- Chemotherapy
- RPM
- PPB
- FDA

advantage of using both continuous and categorical variables, and was thus suitable for the data being analysed. However, it must be noted that this method was developed for larger datasets than the current sample. Thus, in view of the small sample size, this procedure was considered to be strictly exploratory.
Hence, it was deemed that it would not generate any conclusive results, but may lead to useful observations regarding any naturally emerging grouping of the clinical cases.

The two-step cluster method derives its name from the two stage procedure. The first, the ‘preclustering’ stage detects dense clustering regions and identifies outliers that can then be excluded. During the second stage, a chosen distance measure is used as a combination of the likelihoods for the continuous and categorical variables (Everitt et al., 2011).

*Distance measure selection*

The distance between the data points is a central concept in cluster analysis. Several options for the distance measure are available, the most common being the Euclidean distance. The log-likelihood distance measure, which places a probability distribution on the variables, was applied because it permits the use of continuous and categorical variables. An automatic cluster determination algorithm was selected, using Akaike’s Information Criterion (AIC), with up to 15 clusters permitted. AIC provides an estimate for the information lost in a particular model. Thus, a lower AIC value is desirable and reflects the maximal fit of the model to the data.

*Assumption testing*

For the continuous clustering variables (Core language score and Age at diagnosis), the assumption of normality was tested using the Shapiro-Wilk test and upheld ($p > .05$ for all variables). The radiotherapy variable satisfied
the criterion of a multinomial distribution. There were no statistically significant correlations between any of the final clustering variables; thus all of the necessary assumptions for the two-step cluster analysis were satisfied.

6.2.3 Results

6.2.3.1 Participants’ clinical characteristics

In addition to the characteristics already described in the previous chapters, an attempt was made to extract other relevant information from the clinical records, including radiotherapy dose, chemotherapy drugs, pre-operative hydrocephalus, ataxia, and brainstem invasion. Unfortunately, a lot of the relevant information was missing from the patients’ records, limiting further analyses. This highlights the need for a standardized protocol in reporting on different variables that might influence functional outcome in PTF patients. Once clinics adopt a standardized protocol, datasets from different clinics can be combined permitting more large-scale analyses than are currently possible. Table 6.2 provides a summary of all of the information that could be extracted from the records.
Table 6.2

*Patients’ extended clinical history profiles*

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<td>Extent of resection</td>
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<td>P</td>
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<td>NC</td>
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Table 6.2 (continued)

*Patients' extended clinical history profiles*

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*Total dose for the tumour site
6.2.3.2 Exploratory cluster analysis

The AIC value was calculated for a range of models, containing from 2 to 15 clusters (Table 6.3). According to the automatic selection algorithm, two was the optimal number of clusters. However, on examination, in a two-cluster model, radiotherapy was the variable that almost exclusively accounted for the clustering, with very limited influence from CLS and age at diagnosis. This solution was not deemed suitable because with only one clustering variable it would undermine the multivariate nature of the method. The next nearest option, a three-cluster model, was also not suitable due to the large ratio obtained for the largest to smallest clusters (3.3); while the optimal ratio should not exceed the value of three. Finally, the next best solution was a four-cluster model with a cluster size ratio of 2.7 and good cluster quality. Radiotherapy still remained the key clustering variable, but the influence of age at diagnosis and CLS was maximised, in comparison to other models. Thus, the four-cluster solution was selected as the optimal model for the present dataset. The largest cluster contained eight cases and the smallest cluster was comprised of three cases. Two, three and four-cluster models are summarised in Figure 6.2.

The cluster profiles were summarised descriptively, based primarily on the main clustering variables. Other major clinical and outcome variables were also considered when describing the cluster profiles. A summary of these results is presented in Table 6.4 and Figure 6.3.
Table 6.3
Automatic cluster selection algorithm output. Two, three and four-cluster solutions (shaded green) with the lowest AIC values were considered for further analyses

<table>
<thead>
<tr>
<th>Number of clusters in a model</th>
<th>AIC</th>
<th>Ratio of distance measures</th>
</tr>
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<td>2</td>
<td>46.17</td>
<td>4.91</td>
</tr>
<tr>
<td>3</td>
<td>49.85</td>
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</tr>
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<td>1.92</td>
</tr>
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<td>5</td>
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<td>1.11</td>
</tr>
<tr>
<td>6</td>
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<td>2.42</td>
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<td>85.26</td>
<td>1.07</td>
</tr>
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<td>9</td>
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<td>1.21</td>
</tr>
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<td>11</td>
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<td>12</td>
<td>122.05</td>
<td>1.11</td>
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<td>13</td>
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<td>1.31</td>
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<td>14</td>
<td>141.15</td>
<td>1.06</td>
</tr>
<tr>
<td>15</td>
<td>158.78</td>
<td>1.40</td>
</tr>
</tbody>
</table>

Figure 6.2. Contribution of the clustering variables for the two, three and four-cluster solution models. The four-cluster model offers the maximised contribution of every variable
RT – Radiotherapy, CLS – Core Language Score
### Table 6.4

**Case profiling in a four-cluster solution**

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of cases</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Main clustering variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>Yes - 4</td>
<td>Yes - 6</td>
<td>No - 3</td>
<td>No - 8</td>
</tr>
<tr>
<td><strong>Age at diagnosis, months, Y:M (Mdn)</strong></td>
<td>5:7</td>
<td>10:9</td>
<td>16:7</td>
<td>8:2</td>
</tr>
<tr>
<td>Core language Score (Mdn)</td>
<td>74.50</td>
<td>94.00</td>
<td>101.33</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Tumour type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MB</td>
<td>-3</td>
<td>MB</td>
<td>3</td>
<td>AC</td>
</tr>
<tr>
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<td>1</td>
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<td>1</td>
<td>AC</td>
</tr>
<tr>
<td>HGG</td>
<td>-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumour location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVth V</td>
<td>-2</td>
<td>IVth V</td>
<td>-4</td>
<td>LC</td>
</tr>
<tr>
<td>LC</td>
<td>-1</td>
<td>ML</td>
<td>-1</td>
<td>ML</td>
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<tr>
<td>BS</td>
<td>-1</td>
<td></td>
<td></td>
<td>LC</td>
</tr>
<tr>
<td>IVth V</td>
<td>-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-3</td>
<td>Yes</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>-1</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Extent of resection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>NC</td>
<td>-3</td>
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<td>C</td>
</tr>
<tr>
<td>P</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recovery time, Y:M (Mdn)</strong></td>
<td>12:3</td>
<td>6:5</td>
<td>48:11</td>
<td>8:8</td>
</tr>
<tr>
<td><strong>PPB assembly score (Mdn)</strong></td>
<td>28.50</td>
<td>23.50</td>
<td>34.00</td>
<td>23.12</td>
</tr>
<tr>
<td><strong>RPM score (Mdn)</strong></td>
<td>80.00</td>
<td>87.50</td>
<td>95.00</td>
<td>85.00</td>
</tr>
<tr>
<td><strong>FDA score (Mdn)</strong></td>
<td>164</td>
<td>186</td>
<td>193</td>
<td>170</td>
</tr>
</tbody>
</table>


![Figure 6.3. Distribution of cases in a four-cluster solution. The ratio of the largest to the smallest cluster is 2.67](image-url)
In Cluster 1, all patients had received radiotherapy treatment, had the youngest median age at diagnosis and demonstrated the poorest language performance. The majority of the cases (3 out of 4) had a diagnosis of medulloblastoma and had also received adjuvant chemotherapy. These patients also displayed the lowest median non-verbal IQ and most prominent signs of dysarthria. However, the patients in this group had the second longest recovery time and the second highest manual dexterity performance.

In cluster 2, containing 6 cases, all of the patients had also received radiotherapy. However, they were almost twice as old at the time of diagnosis compared to the patients in the first cluster, and had the shortest recovery time. Although language performance in this cluster was the second lowest, it was close to the normative data average for the CELF-5 test. Medulloblastoma accounted for 50% of the cases. All 6 patients had received adjuvant chemotherapy. Their non-verbal IQ was within the average range, but close to one standard deviation below the normative mean. The dysarthria score was second best among all of the clusters, while the manual dexterity score was the second poorest.

Cluster 3 was the smallest, comprised of only three astrocytoma cases. These, however, were the patients that demonstrated the highest performance on the language tests. They were also diagnosed at the oldest median age and had the longest recovery time. Only one out of the three had received chemotherapy treatment. This group
had the best manual dexterity and dysarthria performance, as well as non-verbal IQ (although this was still .33 standard deviations lower compared to the normative mean).

Cluster 4 was the largest in size with eight cases, none of whom had received radiotherapy. Seven of the patients had astrocytoma diagnoses. One medulloblastoma patient in this group had been treated under an experimental protocol without radiotherapy. The majority (7 out of the 8) had not received chemotherapy. Although this group of patients had the second youngest median diagnosis age, their language performance was at the normative population average. They had the second shortest recovery time, second worst dysarthria profile and the worst manual dexterity scores. Their non-verbal IQ was at the borderline level of one SD below the normative population average.

6.2.3.3 Post-hoc correlational analyses

As demonstrated by the cluster analysis, the poorest language skills were observed in patients who had received radiotherapy treatment at the youngest age (Cluster 1). Where patients received radiotherapy at an older age (Cluster 2), their language scores were noticeably higher. In Clusters 3 and 4 patients did not receive radiotherapy and, regardless of the age at diagnosis, their language scores were similar, suggesting that age at diagnosis only matters in the presence of radiotherapy.
The above observations were verified by the post-hoc correlational analysis. This is in accordance to Allen & Goldstein (2014) who recommend that cluster analysis should be followed by a formal statistical evaluation. Correlational analysis revealed that Core Language Score indeed correlated with the age at diagnosis in those patients that received radiotherapy treatment, but not in others (Table 6.5; Figure 6.4).

A further observation, based on the descriptor variables in the cluster analysis, was that higher manual dexterity scores appeared to be associated with the longer recovery time. To verify this, correlational analysis was performed, however, no statistically significant relationship was found ($r = -.06; p = .77$), (Figure 6.5).

Table 6.5

*Association between the age at diagnosis and language (CLS) in radiotherapy-treated (RT) and non-radiotherapy treated (Non-RT) patients*

<table>
<thead>
<tr>
<th>Patient sub-group</th>
<th>Core Language Score, M (SD)</th>
<th>Age at diagnosis, M (SD)</th>
<th>Pearson’s $r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT, N = 10</td>
<td>87.90 (14.43)</td>
<td>35.61 (11.26)</td>
<td>.67</td>
<td>.03*</td>
</tr>
<tr>
<td>Non-RT, N = 11</td>
<td>97.18 (15.89)</td>
<td>62.78 (18.93)</td>
<td>.01</td>
<td>.99</td>
</tr>
</tbody>
</table>
Figure 6.4. Correlation between the age at diagnosis and Core Language Score in radiotherapy-treated (RT) and non-radiotherapy treated (Non-RT) patients. Younger age at diagnosis in RT patients is associated with the diminished language performance.

Figure 6.5. Correlation between the recovery time and Purdue Pegboard Assembly score. No statistically significant associations were observed.
6.3 **Part 2: Diagnosable language disorder, associated speech pathology and neuroimaging markers in PFT survivors**

### 6.3.1 Background

In the neuropsychological investigation, reported in Chapter 3, the patients as a group demonstrated CELF-5 assessment scores that were significantly lower than those of the healthy controls group-matched by age, gender and socio-economic background. However, such a comparison is only possible in the context of a research study. In a clinical setting, normative data from the standardised tests are used as a benchmark for making diagnostic decisions. The classification of patients as deficient or non-deficient on specific functions informs their post-operative rehabilitation management and additional educational support.

In the clinical context, the assessment of speech and language is frequently combined, consistent with a currently dominant school of thought that views these two faculties as complimentary aspects of the communication function. This theoretical model originates from work by Bloom and Lahey (1978) who suggested that linguistic function is underpinned by three key components, including Form, Content and Use (Figure 6.6), and is still widely referred to by researchers and clinicians (e.g., Spanoudis, Natsopoulos, & Panayiotou, 2007; Kesner & Wright, 2013). According to this model, speech is part of the language Form, while its meaning and appropriateness fall into the Content and Use domains.
A comprehensive assessment of speech and language in clinic should ideally include an examination of all components of the language model in order to be able to detect even the most specific and subtle impairments in any of the domains including pragmatics, orientation, interaction, phonological ability, intelligibility, oral motor function, auditory and reading comprehension, verbal and written language production, fluency, hearing, feeding and swallowing (Driver, Ayyangar, & Van Tubbergen, 2015). The current National Institute of Clinical Excellence guidelines recommend that speech and language therapists (SALTs) should be involved in multidisciplinary brain cancer management teams and as part of the rehabilitation services (NICE, 2006). Consequently, speech and language
therapists are best placed to detect any deviations from the norm in speech and language functioning in both the acute and long-term post-treatment phases. At the same time, the assessment tools utilised by SALTs, such as the FDA-2, which was used in the present study, predominantly focus on speech apparatus functioning with little consideration of more complex language functions, such as semantics or pragmatics.

Although there is a notable difference between aphasia and dysarthria, neuroimaging studies (including our findings, reported in Chapter 4) demonstrate overlapping speech and language processing networks, both supra- and infra-tentorially (Hickok & Poeppel, 2001; Price 2012; Marien et al., 2013). In addition, PFT studies have previously pointed out that post-operative mutism, as an acute speech pathology, may predict poor language outcomes in the long-term recovery phase (Hudson et al., 1989; Hudson & Murdoch, 1992; Aarsen et al., 2004). In the following part of the patient-focused investigation we focus on exploring the relationships between the overt oro-motor functioning (as assessed by FDA-2) and higher language processing (as assessed by CELF-5 battery). If a relationship is detected, this would suggest the potential of using dysarthria assessment, carried out in the clinic, as a screening tool for an underlying language disorder.

6.3.2 Method

6.3.2.1 Procedure

Besides the neuropsychological tests described in Chapter
3 (CELF-5, RPM+ and Purdue Pegboard), patients’ oro-motor functioning abilities were assessed using the Frenchay Dysarthria Assessment test, 2nd edition (FDA-2), (Enderby, 1980). The FDA-2 is a tool that is primarily used by speech and language therapists. The researcher was trained by the professional SALT prior to administering this measure with the patients in the present study.

The FDA-2 battery consists of a range of assessment questions and short tasks. Oro-motor functioning is examined in seven domains, including reflexes (cough, swallow, dribble), respiration (at rest and in speech), lips (at rest, spread, seal, alternate, in speech), palate (fluids, maintenance, in speech), laryngeal (time, pitch, volume, in speech), tongue (at rest, protrusion, elevation, lateral, alternate, in speech) and intelligibility (words, sentences, conversation). The FDA-2 manual suggests rating the functional abilities using letters, from ‘e’ (no function) to ‘a’ (perfect function) by filling in a corresponding number of blocks on the assessment sheet. For the purpose of score quantification, in the present study the letters were replaced by numbers from 0 (no function) to 8 (perfect function). This allowed for calculating and comparing the scores with greater precision (Figure 6.7).

6.3.2.2 Identification of a diagnosable language disorder

In Chapter 3 of the present investigation, we have demonstrated that the patients underperformed on the language assessment in comparison to the healthy age-matched control group. However, since the majority of the
scores obtained for the PFT group fell within the low average normative range, the question remains as to whether any of the patients showed evidence of a clinically diagnosable language disorder.

The CELF-5 manual offers a pathway for determining the presence of a diagnosable language disorder. As recommended by the manual, the three most discriminative composite scores are the Core Language Score, the Receptive Language Index and the Expressive Language Index. If any one of these scores falls below 85 (1 SD of the normative mean), further assessment is warranted to determine the nature of the difficulties. The lower the score, the more likely the diagnosis of a language disorder, with the critical diagnostic threshold varying from -1 to -2 SD below the normative mean, according to different sources (Wiig et al., 2013). For the
purpose of the present analysis, any scores below -2SD were classified as severe difficulties, while scores of between -1SD and -2SD were considered to indicate mild difficulties. The patients were then sub-divided into language disorder (LD) and non-language disorder (non-LD) groups. LD group included both mild and severely deficient patients, while in the non-LD group patients performed within or above the norm on all discriminative measured.

**6.3.2.3 Speech deficit analysis, including cerebellar mutism cases**

The average scores were calculated for each domain of the FDA-2 battery (Reflexes, Respiration, Lips, Palate, Laryngeal, Tongue and Intelligibility). A series of Mann-Whitney U-tests was then performed to evaluate the differences between the LD and non-LD sub-groups.

A separate analysis was conducted for the three cerebellar mutism cases identified in the patient cohort. Due to the small number of cases, inferential analyses were not possible and performance profiles were analysed descriptively in relation to the rest of the patient group.

**6.3.2.4 Imaging analysis**

As a separate line of analysis, fMRI and DTI measures were extracted and compared between the patients that exhibited the signs of a language disorder and those that did not. Methodology for obtaining and analyzing fMRI and DTI data is described in Chapters 4 and 5. For the fMRI, individual maps were also obtained showing the metabolic response of each patient during the fMRI task, averaged
across three scans. In addition, 3D high-resolution brain reconstruction was performed using the MRICro software (Rorden & Brett, 2000).

6.3.3 Results

6.3.3.1 Dysarthria profile of the whole patient sample

The FDA-2 manual provides normative data for 14 cerebellar lesion patients, although only as a visual plot without numerical values. The results from the present study were plotted in the same way to compare them to the FDA-2 normative data (Figure 6.8). On visual inspection, overall, the present findings closely resembled those reported by the FDA-2 authors for a cerebellar lesion group. However, in the current study, the patients seemed to demonstrate overall better speech performance in all domains (Respiration, Lips, Palate, Laryngeal and Tongue).

Although the intelligibility of the individual words was lower compared to the normative sample, the intelligibility of the sentences and conversational speech was higher in the present study sample.

The mean scores and standard deviation provide robust estimates of the centrality and spread for normally distributed data. One can assume that the FDA-2 normative data were normally distributed, hence the authors’ decision to use these measures, although this was not mentioned in the manual. The present data, however, on closer examination, were not normally distributed on the vast majority of measures (Shapiro-Wilks’s tests p > .05) with a significant degree of skewness and multiple
outliers. Thus, the means and standard deviations are likely to be poor estimates of the centrality and spread for our data. The median is a measure of centrality that is not sensitive to the outliers and is preferred in cases of a skewed distribution. The median, interquartile ranges and minimum/maximum scores were calculated for the FDA-2 scores in order to obtain a more realistic representation of the central tendencies and variation in the dysarthria scores in the present patient sample (Figure 6.9).

The box plot for which the lowest median scores were obtained was for the Laryngeal functioning domain. In particular, some of the lowest scores were reported in the laryngeal ‘pitch’ function. Other domains where notably low median and minimum scores were observed included swallowing and dribbling reflexes, elevation of the tongue and intelligibility of spoken words. The functions where the fewest number of impairments were detected included the lips spread and rest functions, as well as self-reported palate functioning during the consumption of fluids.
<table>
<thead>
<tr>
<th>Patients in the present study, N = 21</th>
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</thead>
<tbody>
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<td>Reflexes</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
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<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>FDA-2 normative sample of patients with cerebellar lesions, N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflexes</td>
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<td>----------</td>
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<td>4</td>
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<td>5</td>
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</tbody>
</table>

**Figure 6.8.** Comparison of the dysarthria assessment in the present study patient group and the normative FDA-2 sample of cerebellar lesion patients. The normative data table has been copied from the FDA-2 manual. No numeric values for the means and standard deviations are provided in the FDA-2 manual; thus the table was copied exactly as it visually appears. The white horizontal lines represent the mean scores and the areas filled with black represent the spread of the scores around the means (standard deviations) ▲

0 – no function, 8 – no detectable impairment ▼
Figure 6.9. Box plot of the FDA-2 scores. The horizontal markers represent the median scores, the boxes delineate the interquartile ranges (IQR, 25th to 75th percentile), the outer limits of the whiskers demonstrate the maximum and minimum scores. 

○ - an outlier that falls within 1.5 and 3 IQRs

* - an extreme outlier with the score more than 3 IQRs
6.3.3.2 Presence and severity of a diagnosable language disorder in PFT survivors

Table 6.6 presents a summary of the core CELF-5 diagnostic indices for the patient group. Patients that fitted the criteria for further evaluation (below 1SD from the norm average, or scores <= 84) are highlighted in the table and constitute the Language Disorder (LD) sub-group. The remaining patients, whose scores for all three diagnostic indices were above 85, were considered non-LD.

Evidently, eight out of the 21 patients, or 38%, from the

Table 6.6
Key diagnostic CELF-5 scores for PFT survivors

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Core Language Score</th>
<th>Receptive Language Index</th>
<th>Expressive Language Index</th>
<th>Further investigation required?</th>
</tr>
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<tbody>
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<td>C8</td>
<td>65</td>
<td>65</td>
<td>71</td>
<td>Yes</td>
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<td>R8</td>
<td>80</td>
<td>67</td>
<td>91</td>
<td>Yes</td>
</tr>
<tr>
<td>D7</td>
<td>89</td>
<td>84</td>
<td>87</td>
<td>Yes</td>
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<td>E68</td>
<td>113</td>
<td>112</td>
<td>108</td>
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<td>A8</td>
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<td>95</td>
<td>No</td>
</tr>
<tr>
<td>U8</td>
<td>93</td>
<td>96</td>
<td>102</td>
<td>No</td>
</tr>
<tr>
<td>E4</td>
<td>124</td>
<td>116</td>
<td>95</td>
<td>No</td>
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<td>75</td>
<td>Yes</td>
</tr>
<tr>
<td>C7</td>
<td>95</td>
<td>98</td>
<td>104</td>
<td>No</td>
</tr>
<tr>
<td>S6</td>
<td>108</td>
<td>102</td>
<td>104</td>
<td>No</td>
</tr>
<tr>
<td>J7</td>
<td>99</td>
<td>92</td>
<td>98</td>
<td>No</td>
</tr>
<tr>
<td>S7</td>
<td>93</td>
<td>98</td>
<td>89</td>
<td>No</td>
</tr>
<tr>
<td>R7</td>
<td>70</td>
<td>61</td>
<td>75</td>
<td>Yes</td>
</tr>
<tr>
<td>S4</td>
<td>80</td>
<td>77</td>
<td>85</td>
<td>Yes</td>
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<tr>
<td>M48</td>
<td>106</td>
<td>106</td>
<td>93</td>
<td>No</td>
</tr>
<tr>
<td>A9</td>
<td>91</td>
<td>92</td>
<td>83</td>
<td>Yes</td>
</tr>
<tr>
<td>M78</td>
<td>79</td>
<td>88</td>
<td>83</td>
<td>Yes</td>
</tr>
<tr>
<td>E58</td>
<td>100</td>
<td>92</td>
<td>89</td>
<td>No</td>
</tr>
<tr>
<td>C9</td>
<td>101</td>
<td>100</td>
<td>100</td>
<td>No</td>
</tr>
<tr>
<td>I9</td>
<td>91</td>
<td>86</td>
<td>85</td>
<td>No</td>
</tr>
</tbody>
</table>
present study met the criteria for further investigation and possible diagnosis of a language disorder. For a more precise description of the nature of the observed deficits, Table 6.7 details whether the difficulties were observed in one of the domains or both. If a score fell between 1 and 2SD below the normative population mean (between 70 and 84), the deficit was labelled as ‘mild-moderate’. If a score fell 2 SD below the normative mean (below 69), the deficit was labelled as ‘severe’.

Table 6.7

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Nature of the language deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8</td>
<td>Severe receptive/Mild-moderate expressive</td>
</tr>
<tr>
<td>R8</td>
<td>Severe receptive</td>
</tr>
<tr>
<td>D7</td>
<td>Mild-moderate receptive</td>
</tr>
<tr>
<td>L6</td>
<td>Severe receptive/Mild-moderate expressive</td>
</tr>
<tr>
<td>R7</td>
<td>Severe receptive/Mild-moderate expressive</td>
</tr>
<tr>
<td>S4</td>
<td>Mild-moderate receptive</td>
</tr>
<tr>
<td>A9</td>
<td>Mild-moderate expressive</td>
</tr>
<tr>
<td>M78</td>
<td>Mild-moderate expressive</td>
</tr>
</tbody>
</table>

6.3.3.3 Dysarthria profiles in patients displaying signs of a language disorder

Oro-motor functioning was compared between the LF and non-LD sub-groups, and the results are presented in Table 6.8. Those PFT patients that displayed signs of a language disorder also had a detectable reduction in the regulation of their oromotor reflexes (coughing, swallowing, dribbling) and reduced intelligibility of speech, compared to the patients without detectable signs of a language disorder. The regulation of respiration, and the laryngeal, lips, palate, and tongue functions was not significantly different between the LD and non-LD sub-groups.
Table 6.8
Comparison of the FDA mean scores for different areas of oromotor functioning between PFT patients with and without the signs of a language disorder

<table>
<thead>
<tr>
<th>FDA-2 scores, Mean (SD)</th>
<th>LD PFT patients N = 8</th>
<th>Non-LD PFT patients N = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflexes</td>
<td>5.08 (1.39)</td>
<td>7.26 (.88)</td>
</tr>
<tr>
<td>Respiration</td>
<td>6.13 (1.03)</td>
<td>7.08 (1.08)</td>
</tr>
<tr>
<td>Lips</td>
<td>7.10 (.56)</td>
<td>7.37 (.68)</td>
</tr>
<tr>
<td>Palate</td>
<td>6.96 (.58)</td>
<td>7.54 (.70)</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>5.84 (1.08)</td>
<td>6.19 (1.13)</td>
</tr>
<tr>
<td>Tongue</td>
<td>6.92 (.68)</td>
<td>7.13 (.68)</td>
</tr>
<tr>
<td>Intelligibility</td>
<td>5.58 (1.54)</td>
<td>7.38 (.68)</td>
</tr>
</tbody>
</table>

Test of significance

<table>
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<tr>
<th></th>
<th>.002**</th>
<th>.07</th>
<th>.24</th>
<th>.02*</th>
<th>.42</th>
<th>.66</th>
<th>.006**</th>
</tr>
</thead>
<tbody>
<tr>
<td>z</td>
<td>2.95</td>
<td>1.85</td>
<td>1.22</td>
<td>2.27</td>
<td>.84</td>
<td>.47</td>
<td>2.69</td>
</tr>
</tbody>
</table>

Effect size, r

|                  | .65    | .40  | .26  | .50   | .18  | .10  | .59    |

LD – language disorder
Mann-Whitney U-test, two-tailed
*Significant at p = .05 uncorrected
** Significant after the familywise error correction
Effect size $r = \frac{Z}{\sqrt{N}}$

6.3.3.4 Functional outcomes in patients with a history of post-operative mutism

In the present sample, three patients (14%) had cerebellar mutism (CM) post-surgery. Notable, only one of them was in the LD sub-group, based on the CELF-5 scores. This sub-group of patients deserves separate discussion as the long-term functional outcomes of CM are still largely unknown. Table 6.9 presents the clinical characteristics and outcomes of the language, cognitive, manual dexterity and dysarthria assessment. The patient with the longest duration of mutism (3 months) also had the worst language and manual dexterity outcomes, as well as the least intelligible speech. Conversely, the patient who was the oldest at the time of diagnosis
demonstrated near average language performance, but the lowest non-verbal intelligence score. Interestingly, all three patients with a history of mutism demonstrated notable deficits in the regulation of the oro-motor reflexes, which include coughing, swallowing and involuntary dribbling. A whole-group analysis of the FDA-2 scores demonstrated that poor regulation of reflexes was significantly more pronounced in patients with signs of a language disorder. Thus, there may be a relationship between mutism, reflex regulation and long-term language impairments, which should be investigated in larger sample studies.

6.3.3.5 Imaging markers of a language disorder

Neuroimaging data were available for four LD and twelve non-LD patients. Structurally, significant abnormalities of the posterior fossa were evident in the majority of the patients when compared to healthy controls. Figure 6.10 presents an example of the high-resolution anatomical reconstruction of the brain of a healthy volunteer. Figures 6.11A-B demonstrate reconstruction of the brain anatomy of the patients that displayed the signs of a language disorder on CELF-5 assessment, while Figures 6.12A-F show the brain anatomy reconstruction of the patients with no overt signs of a language disorder.

During the fMRI task, there was no significant difference in the average number of voxels where signal increased above the set threshold of $z = 2.3$ in relation to the individual baseline between LD and non-LD sub-groups (Table 6.10, Figures 6.13 and 6.14). However, when the DTI scalars were compared, LD group demonstrated significantly reduced FA index within the left Arcuate Fasciculus (Table 6.11).
# Table 6.9

**Clinical characteristics and assessment outcomes of the patients with a history of post-operative mutism**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>C8</th>
<th>S7</th>
<th>S4</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Duration of speech absence</td>
<td>3 months</td>
<td>3 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Age at diagnosis, Y:M</td>
<td>4:7</td>
<td>12:9</td>
<td>4:7</td>
</tr>
<tr>
<td>Recovery Period, Y:M</td>
<td>12:6</td>
<td>5:2</td>
<td>16:10</td>
</tr>
<tr>
<td>Tumour type</td>
<td>MB</td>
<td>MB</td>
<td>AC</td>
</tr>
<tr>
<td>Tumour location</td>
<td>4th ventricle</td>
<td>4th ventricle</td>
<td>?</td>
</tr>
<tr>
<td>Extent of resection</td>
<td>Complete</td>
<td>Near complete</td>
<td>Partial</td>
</tr>
<tr>
<td>Dominant hand</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Assessment score / standardised z-score</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-verbal intelligence: RPM</td>
<td>80 / -.28</td>
<td>60 / <strong>-1.40</strong></td>
<td>85 / 0</td>
</tr>
<tr>
<td>Language: CELF-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core Language Score</td>
<td>65 / <strong>-1.78</strong></td>
<td>93 / .02</td>
<td>80 / -.82</td>
</tr>
<tr>
<td>Receptive Language Index</td>
<td>65 / <strong>-1.60</strong></td>
<td>98 / .48</td>
<td>77 / -.84</td>
</tr>
<tr>
<td>Expressive Language Index</td>
<td>71 / <strong>-1.95</strong></td>
<td>89 / -.18</td>
<td>85 / -.57</td>
</tr>
<tr>
<td>Language Content Index</td>
<td>63 / <strong>-1.50</strong></td>
<td>90 / .34</td>
<td>78 / -.48</td>
</tr>
<tr>
<td>Language Memory Index</td>
<td>75 / <strong>-1.46</strong></td>
<td>89 / -.37</td>
<td>85 / -.68</td>
</tr>
<tr>
<td>Manual dexterity: Purdue Pegboard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand</td>
<td>6 / <strong>-1.79</strong></td>
<td>11 / -.11</td>
<td>13 / .56</td>
</tr>
<tr>
<td>Non-dominant hand</td>
<td>9 / -.22</td>
<td>7 / -.77</td>
<td>12 / .60</td>
</tr>
<tr>
<td>Two-hand score</td>
<td>6 / -.54</td>
<td>5 / -.83</td>
<td>9 / .33</td>
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<tr>
<td>Assembly score</td>
<td>17 / -.81</td>
<td>16 / -.92</td>
<td>22 / -.26</td>
</tr>
<tr>
<td>Oro-motor functioning: FDA-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>4.67 / <strong>-1.16</strong></td>
<td>5.33 / -.72</td>
<td>4.00 / <strong>-1.60</strong></td>
</tr>
<tr>
<td>Respiration</td>
<td>6.00 / -.63</td>
<td>6.50 / -.19</td>
<td>8.00 / <strong>1.13</strong></td>
</tr>
<tr>
<td>Lips</td>
<td>7.60 / .52</td>
<td>7.80 / .84</td>
<td>7.80 / .84</td>
</tr>
<tr>
<td>Palate</td>
<td>7.67 / .50</td>
<td>8.00 / .97</td>
<td>6.33 / <strong>-1.40</strong></td>
</tr>
<tr>
<td>Laryngeal</td>
<td>6.50 / .40</td>
<td>6.00 / -.05</td>
<td>5.25 / -.74</td>
</tr>
<tr>
<td>Tongue</td>
<td>7.33 / .43</td>
<td>7.17 / .18</td>
<td>7.33 / .43</td>
</tr>
<tr>
<td>Intelligibility</td>
<td>3.33 / <strong>-2.43</strong></td>
<td>8.00 / .94</td>
<td>7.00 / .22</td>
</tr>
</tbody>
</table>

*The standardised z-score reflects the displacement of a score by the number of standard deviations in relation to the PFT group mean*

MB – medulloblastoma, AC – astrocytoma, ? – no data available

Bold font – scores deviating from the PFT group mean by more than 1SD
Figure 6.10. Example of the high-resolution anatomical reconstruction of a healthy volunteer’s brain
Figure 6.11A. High-resolution reconstruction of a brain anatomy of the patients displaying overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.11B. High-resolution reconstruction of a brain anatomy of the patients displaying overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12A. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12B. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12C. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12D. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12E. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Figure 6.12f. High-resolution reconstruction of a brain anatomy of the patients displaying no overt signs of a language disorder. Lesions of the posterior fossa are evident, when compared to the normal anatomy of a healthy volunteer shown in Figure 6.8.
Table 6.10
Average number of voxels activated above the set threshold $z = 2.3$ in LD and non-LD patients during Semantic Retrieval and Covert Articulation conditions

<table>
<thead>
<tr>
<th></th>
<th>Semantic Retrieval, M (SD)</th>
<th>Covert Articulation, M (SD)</th>
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<tbody>
<tr>
<td>LD patients, n = 4</td>
<td>35196 (20959)</td>
<td>17449 (14391)</td>
</tr>
<tr>
<td>Non-LD patients, n = 12</td>
<td>44278 (25381)</td>
<td>17694 (11787)</td>
</tr>
<tr>
<td>Test of significance*, $p$</td>
<td>.52</td>
<td>.88</td>
</tr>
<tr>
<td>$z$</td>
<td>-.728</td>
<td>-.182</td>
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<td>Effect size, $r$</td>
<td>.18</td>
<td>.05</td>
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*Mann-Whitney U-tests, two-tailed
Effect size $= Z/\sqrt{N}$

Figure 6.13. Patterns of cortical activation in patients during the Semantic Retrieval condition of the fMRI task, overlaid on their anatomical scans
Figure 6.14. Patterns of cortical activation in patients during the Covert Articulation condition of the fMRI task, overlaid on their anatomical scans
Table 6.11
DTI indices in LD and non-LD patients across the regions of interest (ROIs) described in Chapter 5, including whole brain (global), bilateral arcuate fasciculus and bilateral superior cerebellar peduncle.

<table>
<thead>
<tr>
<th>Scalar</th>
<th>ROI</th>
<th>LD patients, N = 4 M (SD)</th>
<th>Non-LD patients, N =12 M (SD)</th>
<th>p</th>
<th>z</th>
<th>r</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global</td>
<td>.41 (.02)</td>
<td>.42 (.01)</td>
<td>.09</td>
<td>-1.44</td>
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<tr>
<td></td>
<td>FA</td>
<td>Left AF</td>
<td>.33 (.01)</td>
<td>.35 (.01)</td>
<td>.02*</td>
<td>-2.09</td>
</tr>
<tr>
<td></td>
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<td>Right AF</td>
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<td>.33 (.01)</td>
<td>.17</td>
<td>-1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left SCP</td>
<td>.58 (.04)</td>
<td>.59 (.03)</td>
<td>.48</td>
<td>-.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right SCP</td>
<td>.58 (.03)</td>
<td>.59 (.04)</td>
<td>.17</td>
<td>-1.04</td>
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<tr>
<td></td>
<td>MD, E-3 mm²/s</td>
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<td>.79 (.04)</td>
<td>.79 (.02)</td>
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<td>-.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left AF</td>
<td>.75 (.03)</td>
<td>.74 (.03)</td>
<td>.33</td>
<td>-.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right AF</td>
<td>.75 (.02)</td>
<td>.75 (.02)</td>
<td>.43</td>
<td>-.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left SCP</td>
<td>.79 (.09)</td>
<td>.80 (.04)</td>
<td>.21</td>
<td>-.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right SCP</td>
<td>.80 (.09)</td>
<td>.80 (.04)</td>
<td>.21</td>
<td>-.91</td>
</tr>
<tr>
<td></td>
<td>AD, E-3 mm²/s</td>
<td>Global</td>
<td>1.16 (.04)</td>
<td>1.18 (.03)</td>
<td>.29</td>
<td>-.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left AF</td>
<td>1.01 (.03)</td>
<td>1.02 (.04)</td>
<td>.43</td>
<td>-.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right AF</td>
<td>1.01 (.02)</td>
<td>1.02 (.03)</td>
<td>.43</td>
<td>-.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left SCP</td>
<td>1.36 (.12)</td>
<td>1.40 (.08)</td>
<td>.37</td>
<td>-.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right SCP</td>
<td>1.39 (.13)</td>
<td>1.41 (.09)</td>
<td>.17</td>
<td>-1.04</td>
</tr>
<tr>
<td></td>
<td>RD, E-3 mm²/s</td>
<td>Global</td>
<td>.70 (.05)</td>
<td>.68 (.04)</td>
<td>.33</td>
<td>-.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left AF</td>
<td>.73 (.03)</td>
<td>.70 (.03)</td>
<td>.07</td>
<td>-1.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right AF</td>
<td>.72 (.03)</td>
<td>.70 (.03)</td>
<td>.25</td>
<td>-.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left SCP</td>
<td>.60 (.01)</td>
<td>.59 (.06)</td>
<td>.48</td>
<td>-.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right SCP</td>
<td>.60 (.08)</td>
<td>.59 (.06)</td>
<td>.38</td>
<td>-.40</td>
</tr>
</tbody>
</table>

Note. Mann-Whitney U-tests, one-tailed.
* Significant at p = .05, uncorrected
Effect size r = Z/\sqrt{N}

6.4 Discussion

6.4.1 Younger age at diagnosis is associated with the poorer language outcomes in radiotherapy-treated patients

The present investigation explored paediatric PFT clinical history factors that may be related to language functioning
in the long-term recovery phase. As the sample size did not permit reliable predictive modelling, exploratory cluster analysis was performed in order to identify naturally emerging groups of cases with shared characteristics. In our sample of 21 patients, the analysis revealed four clusters with a number of similar clinical and outcome features.

Radiotherapy status was the clustering variable that determined group membership most strongly in all of the evaluated cluster solutions, suggesting that language outcomes are very closely associated with the history of irradiation. This is in agreement with the findings from the systematic literature review (Chapter 2) that reported an association between radiotherapy treatment and adverse long-term language outcomes (Hudson & Murdoch, 1992; Copeland et al., 1999; Edelstein et al., 2011; Huber et al., 2007), confirming once again that structural damage caused by radiotherapy has a long-term impact on the developing brain with serious functional consequences.

Perhaps even more importantly, the cluster analysis revealed that a younger age at diagnosis was associated with negative consequences for language performance. As discussed in the systematic literature review, the current evidence in this regard is mixed and sometimes even contradictory. While some studies report that a younger age at diagnosis is associated with negative outcomes (Vaquero et al., 2008; Edelstein et al., 2011), others report no clear relationship (Huber et al., 2007; Morgan et al., 2011) or even a positive association in the event of the
absence of adjuvant treatment (Copeland et al., 1999). Our findings seem to support the ‘growing into deficit’ theory, which suggests that the consequences of brain damage early in life may only become apparent and progressively severe as the environmental demands increase, and more complex cognitive functions are expected to mature (Aarsen et al., 2006; de Beer & Scheltens, 2016). This highlights the importance of long-term monitoring of patients’ development, as the full impact of brain tumours on linguistic function may not become obvious until much later in the recovery phase.

6.4.2 Duration of recovery period and manual dexterity

A further observation from the descriptor variables in cluster analysis was the improved manual dexterity performance in patients with the longest recovery time. However, this relationship was non-significant on the post-hoc correlational analysis. Whether the relationship is absent or simply could not have been detected with such small sample, is yet to be determined in larger studies. Nevertheless, a number of studies have reported the link between the duration of recovery and improvement in manual dexterity. For example, Rueckriegel et al. (2009) in a study of 41 patients found a high degree of association between the short recovery time and impaired kinematic parameters in both medulloblastoma and astrocytoma patients. Callu et al. (2009) observed a gradual improvement in the upper limb motor function in twelve patients during the first year following PFT treatment. The authors attributed this finding to the
dynamic functional reorganisation of the motor control network with the recruitment of the peri-lesional and distal neural tissue, which has previously been demonstrated in traumatic brain injury and stroke patients (Askim, Indredavik, Vangberg, & Håberg, 2009; Caeyenberghs, Wenderoth, Smits-Engelsman, Sunaert, & Swinnen, 2009). The literature, therefore, suggests that linguistic and motor recover may follow different long-term trajectories; while the ‘growing into deficit’ is likely in terms of language skills, motor recovery may follows a more favourable path.

### 6.4.3 Speech difficulties as an indication of an underlying language disorder in PFT survivors

In the present sample, over a third of the patients met the CELF-5 criteria for a diagnosable language disorder (LD) in the receptive and/or expressive domains. Notably, the LD patients also had significantly reduced intelligibility of speech. These findings suggest that oro-motor functioning difficulties can serve as an indicator of an underlying language disorder, although this does not imply a cause-effect relationship. Other studies have previously demonstrated that speech pathology predicts language processing difficulties. Previously, impaired speech perception and poor phonological awareness have been linked to Specific Language Impairment (SLI), developmental dyslexia and literacy development (Ziegler, Pech-George, George, Alario, & Lorenzi, 2005; Robertson, Joanisse, Desroches, & Ng, 2009; Vanderwalle, Boets, Ghesquiere, & Zink, 2011). Although these studies have focused on the perception of an external auditory input, it is likely that poor perception of own speech can also lead
to reduced intelligibility, which was evident in the present study sample.

Another domain where LD patients have demonstrated significantly diminished functioning is reflex control, including swallowing, coughing and involuntary dribbling. These reflexes draw on a number of physiological components, including oral motor regulation, as well as pharyngeal, esophageal, respiratory and gastrointestinal functions (Driver, Ayyangar, & Van Tubbergen, 2015). Thus, a child lacking swallowing ability is likely to have reduced control of their speech production apparatus overall, leading to diminished expressive language. The present findings demonstrate the utility of the dysarthria assessment as a screening tool for potential signs of a language disorder, which is extremely important in a clinical context where patients’ health conditions and time constraints may not always permit comprehensive language assessment.

6.4.4 Post-operative cerebellar mutism and long-term speech and language outcomes

In the present study, the cerebellar mutism patients have been discussed separately, as the long-term impact of this complication is still not understood. Three patients in our cohort of 21 (14%) had a history of post-operative mutism, which is within the estimated incidence of mutism, reported to be between 8% and 30% (De Smet et al., 2007). Two of the patients in our study were mute for three days post surgery, while one had experienced a prolonged period of muteness of three months. Evidently,
the patient with the longest duration of mutism also had the lowest language scores, poorest intelligibility of speech and diminished oro-motor reflex control.

A second patient with the history of mutism who was diagnosed at the same age as the first one but was only mute for three days, demonstrated language scores below the PFT group average, although within -1SD. Unlike the first patient, however, they did not undergo radiotherapy or chemotherapy treatment. Finally, a third patient, who was also mute for three days but diagnosed at a much older age compared to the first two, displayed language scores close to the average, despite receiving both radiotherapy and chemotherapy.

Several studies discussed in the literature review (Chapter 2) reported a link between cerebellar mutism and adverse long-term language outcomes (Hudson et al., 1989; Hudson & Murdoch, 1992; Aarsen et al., 2004). However, in the present study, for the first time we have highlighted the link between the duration of mutism and speech and language abilities. In addition, adjuvant treatment and a younger age at diagnosis are likely to further exacerbate post-mutism language deficits, mirroring the findings from the cluster analysis in relation to the whole PFT sample.

In the present study, the patients’ pre-morbid level of language proficiency is not known. Yet, a study by Di Rocco et al (2011) suggested that this can be a significant factor in the development of mutism. In a prospective study of 34 children diagnosed with PFT, the authors reported that a pre-operative language impairment is a
primary risk factor for post-surgery mutism. Interestingly, they argued that surgery may actually improve the linguistic abilities of some patients. Our findings, in conjunction with the published literature, suggest that there is still much to be explored when it comes to the long-term language functioning of the sub-group of PFT children with a history of mutism. While in itself it is highly likely to be an adverse factor, a number of moderating variables should also be considered, including the duration of mutism, adjuvant treatment, age at diagnosis and pre-morbid language impairments.

6.4.5 Structural and functional imaging markers of a language disorder in PFT survivors

Our study is the first one in the field to investigate functional and structural differences between those PFT survivors that display the signs of a diagnosable language disorder and those that do not. High-resolution reconstruction of the brain anatomy revealed significant gross abnormalities in many of the patients. Yet, these abnormalities did not necessarily correspond to the deficits in the overt language performance. For example, patient C9 who only had left cerebellar hemisphere preserved, demonstrated normal performance on CELF-5 tests. At the same time, patient L6 with seemingly preserved cerebellum exhibited some of the poorest language performance. In the past, studies have suggested that cerebellar volume is predictive of the cognitive performance (Marien et al., 2014). Although we did not formally quantify the volume of this structure and our
sample size is very small, qualitative evaluation of the brain reconstruction suggests that amount of cerebellar volume preserved may not be a reliable indicator of the overt performance, and other factors should be investigated.

Individual fMRI maps for both Semantic Retrieval and Covert Articulation conditions revealed substantial between-subject variability in BOLD response. However, the patterns of activation were consistent with the results reported in Chapter 4. Specifically, in the semantic condition activation was more widespread compared to the articulation condition, for both LD and non-LD patients. When the number of active voxels was compared between these two sub-groups, no statistical difference was detected, although the trend was towards more widespread activation in the non-LD group. These observations must be interpreted with caution, as our sample size permitted sufficient power to detect only large effect sizes above .7, assuming critical significance level of .05 and a two-tailed test, according to the calculations using G*Power 3.9.1 software (Faul, Erdfelder, Lang & Buchner, 2007). Thus, a larger sample is required to produce reliable findings.

Comparison of the DTI metrics revealed statistically significant reduction of the FA index within the left arcuate fasciculus in LD patients. One of the surprising findings from the DTI study reported in Chapter 5 was that patients as a group did not show differences in this metric within the left arcuate fasciculus when compared to healthy controls, contrary to the known importance of this structure in language processing. Findings from the
patient-focused investigation reported in this chapter suggest that reduction of the FA within the arcuate fasciculus may indeed take place, but it is only detectable when LD patients are isolated as a separate sub-group. Similarly to the fMRI results, these findings must be interpreted with caution due to the small sample size, and larger replication studies are warranted.

6.4.6 Limitations of the study

The present study is limited in a number of ways that must be considered for the unbiased interpretation of the findings. First of all, a large number of missing data points precluded the consideration of a number of potentially important variables in the analysis, such as pre-operative hydrocephalus, ataxia and brainstem invasion. These factors have previously been discussed in the literature as potentially relevant to adverse functional outcomes, and must be included in the analysis if a full appreciation of the clinical factors’ influence on the long-term recovery course is to be achieved. Similarly, no records were available regarding whether any of the patients received speech and language therapy as part of their post-operative management, and it was assumed that none did. However, if this information was wrongly omitted from the records, this would have biased the obtained results.

The conclusions that can be drawn from the cluster analysis are also limited as this is purely an explorative procedure, which is not able to indicate any causal inference. Cluster analysis is best suited to generating
data-driven observations that can be further explored with hypothesis-driven methods. However, as mentioned previously, the sample size of a present study is not large enough for reliable predictive modelling; thus, cluster analysis was chosen as a suitable alternative for evaluation of the relationship between clinical history factors and functional outcomes.

### 6.4.7 Conclusions

In summary, the present study demonstrated the utility of the cluster analysis method as an exploratory, data-driven approach to analysing the findings from smaller cohort studies where predictive modelling, such as regression, is not reliable. In a cohort of 21 long-term PFT survivors, four prominent clusters were identified, based on language performance and several clinical history features. Two clusters were particularly distinct in terms of their language profiles. Specifically, the cluster of patients that were diagnosed at the youngest age and received radiotherapy treatment displayed the poorest language performance. At the same time, the best language outcomes were observed in the patients that were diagnosed at the oldest age and did not receive radiotherapy. Post-hoc analysis confirmed that younger age at diagnosis is associated with diminished language skills in radiotherapy-treated patients, but not in those who did not receive adjuvant radiotherapy.

Over a third of the patients demonstrated prominent signs of a language disorder in the expressive and/or receptive language domains. There was a notable relationship
between the presence of a language disorder and signs of chronic dysarthria; specifically, reduced reflex control and intelligibility of speech. A prolonged duration of post-operative mutism appeared to be associated with particularly poor language performance, although this observation was based only on three cases of mutism, so further verification is warranted.

Finally, the first of its kind investigation of the neuroimaging markers of the language deficits in PFT survivors revealed no metabolic response differences, but a reduction in the fractional anisotropy within the left arcuate fasciculus in those patients who displayed clinically significant signs of a language disorder.

To summarise, the present study convincingly demonstrated high prevalence of the clinically significant long-term language deficits in the PFT population with a detectable neuroimaging marker. It also highlighted related clinical history factors and easily observable changes in the speech apparatus functioning that could alert clinicians to a possible underlying language disorder in patients, thus allowing timely intervention.
Chapter 7: General discussion

Key points

- Long-lasting language processing deficits should be recognised as a complication of the PFT treatment that occurs in a large proportion of patients;
- PFT survivors highlight communication difficulties as a major cause of anxiety and social withdrawal;
- Avoidance or reduced dose radiotherapy remain the most reliable methods of prevention in regard to long-term neurocognitive sequelae;
- Pharmacological treatment with psychoactive and sedative drugs in the acute post-operative stage may help to alleviate severe posterior fossa syndrome symptoms, including speech disturbances;
- In the long-term recovery phase, the aim of the pharmacological and behavioural interventions is to improve neurocognitive functioning;
- Restorative behavioural approaches, based on repeated practice, are most effective in long-term language rehabilitation;
- Modern non-invasive neuroimaging techniques offer means for future in-depth exploration of the metabolic, microstructural and biochemical neural changes underpinning communication deficits in long-term PFT survivors.

7.1. Introduction

Almost three decades ago, Schmahmann (1991) put forward ideas about the importance of the cerebellum in the modulation of non-motor functions, including linguistic processing. It was also around that time that pioneer
researchers began to document language processing deficits in PFT patients, beyond motoric aspects of speech (Hudson et al., 1989; Hudson & Murdoch, 1992). Finally, also in the early 1990s, fMRI emerged as a new powerful method of studying language function dynamically and non-invasively (Ogawa et al., 1990). Due to these key developments, scientists and clinicians now possess a wealth of knowledge about the cerebellar linguistic topography, specific speech and language deficits observable in cerebellar tumour patients, and a range of factors that are likely to predispose patients to poor outcomes. It is, therefore, timely for the scientific discourse to change from debating whether PFT patients indeed experience long-lasting language deficits, to acknowledging these as a frequent complication that requires effective management. This calls for a joint effort of the research and clinical communities in order to develop an understanding of the neural bases of language recovery in this group of patients, and implement individualised rehabilitation interventions.

The following discussion will provide an overview of the current understanding of the speech and language rehabilitation needs of PFT survivors. Current pharmacological and behavioural approaches to the management of neurocognitive and communication difficulties will be discussed, both in the acute and long-term stages of recovery. Finally, future research directions in this area will be discussed with an emphasis on the use of advanced neuroimaging techniques.

7.2 Speech and language rehabilitation needs of PFT survivors

The need for language rehabilitation in the PFT population is
indicated by the prevalence of long-lasting deficits in a large proportion of survivors. Indeed, while the reported prevalence of speech, language and communication needs among school pupils in England is around 21% (Department for Education, 2016), in our study sample 38% of the patients displayed some form of language processing deficit.

In 2015, an independent Cancer Taskforce published a document entitled ‘Achieving word-class cancer outcomes: a strategy for England 2015-2020’. While the main aim of the document was to improve cancer survival rates, it also addressed issues pertaining to the long-term survivorship of paediatric cancers. The document acknowledges the long-term psychological and psychical consequences of childhood cancer, which last into adulthood. Yet, it is pointed out that the current follow-up pathways often lack continuity in those centres where children’s services cease at the age of 16, and adult services do not commence until the age of 18. In addition, there seems to be a lack of understanding among health professionals about how comorbid complications should be managed, including those arising long after the completion of the treatment. In the light of this, one of the recommendations states that “NHS England should ask NIHR and research charities to develop research protocols which would lead to a much better understanding of the long-term consequences of different treatment options, including patient experience and quality of life considerations” (Cancer Taskforce, 2015, p.58).

Long-term communication deficits in PFT survivors fall precisely into the category of delayed impact deficits with a lack of structured rehabilitation support. Unmet rehabilitation
needs can lead to a range of behavioural and academic difficulties. Kieffer et al. (2012) gathered teachers’ views on the re-integration of 29 PFT patients into the education system and found that, in comparison to their healthy peers, the patients were more likely to present with learning difficulties and display asocial and disturbing behaviour. Moreover, brain tumour patients themselves name speech and language difficulties as a major cause of social withdrawal and psychological distress. In 2016, The Brain Tumour Charity published a report ‘Losing my place: the reality of childhood with a brain tumour’, based on a survey of 282 children and young people. 70% of the respondents reported missing out on socialising with friends. When talking about avoiding social situations, participants cited reasons such as not being able to understand what people are saying when there is a background noise, struggling to formulate thoughts, and getting mixed up with words (The Brain Tumour Charity, 2016b). An earlier study of 1017 adults, diagnosed with a brain tumour either in childhood or adulthood, revealed that one in five continue to have profound aphasia and/or speech difficulties that leave them anxious, embarrassed and scared of appearing ‘thick’ or ‘drunk’ (The Brain Tumour Charity, 2015). Thus, the need for treatment and management of these long-term communication impairments is evident from both patients’ own subjective accounts and from objective measurement-based studies, including the one reported in this thesis.

7.3 Prevention and re-mediation of the long-term communication impairments in PFT survivors

The avoidance of radiotherapy in children under the age of
three and the application of a reduced irradiation dose in older children remain the most reliable approaches to preventing long-term cognitive and linguistic deficits (Ajithkumar, Price, Horan, Burke, & Jefferies, 2017). Where such strategies are not possible, pharmacological and behavioural interventions have been trialled for re-mediation of neurocognitive sequelae in the acute and long-term recovery stages.

### 7.3.1 Pharmacological interventions

Pharmacological treatments of post-PFT neuropsychological and behavioural complications have been applied in the immediate post-operative period to resolve symptoms of cerebellar mutism, and in the long-term recovery phase for the improvement of overall neurocognitive functioning. It must be noted, however, that such treatments are usually administered at the discretion of clinicians in individual cases and currently no standard protocols exist for the treatment of posterior fossa syndrome, cerebellar mutism or long-lasting cognitive impairments. In the acute or sub-acute phase, pharmacological treatment is only administered in cases where symptoms cause significant distress and interfere with normal recovery (Lanier & Abrams, 2017).

Among the drugs reported to have a positive impact on agitation, disorientation, emotional liability and speech pathology are antipsychotic medications such as aripiprazole, olanzapine, risperidone and carbamazepine (Turkel et al., 2004; Yap et al., 2012; Lanier & Abrams, 2017), and sedatives such as zolpidem, lorazepam and clonazepam (Shyu et al, 2011; Lanier & Abrams, 2017). Despite some positive findings, to date there have been no large scale systematic studies investigating the efficacy of these drugs for the
treatment of acute post-surgery complications in PFT survivors.

Similarly, no standard protocols exist for the drug treatment of neurocognitive sequelae in the long-term recovery phase. Several studies have reported positive effects of methylphenidate, a central nervous system stimulant, commonly prescribed for the treatment of ADHD (DeLong, Friedman, Friedman, Gustafson, & Oakes, 1992; Meyers, Weitzner, Valentine, & Levin, 1998; Thompson et al., 2001; Mulhern et al., 2004; Gehring et al., 2012). However, the patient samples in these studies were mixed and included both infra- and supra-tentorial tumours, as well as leukaemia survivors. Thus, at present it is difficult to make firm conclusions about the benefits of methylphenidate for PFT patients. In addition, the effects of this stimulant are only observable during its use and do not result in lasting sustained improvement, undermining its utility for long-term rehabilitation (Lassaletta et al., 2015).

Another drug that has recently been investigated in the context of ameliorating the long-term neurocognitive effects of brain tumours is donepezil, a selective acetylcholinesterase inhibitor. It is most frequently used in Alzheimer’s disease patients and works by increasing acetylcholine signalling through slowing its synaptic degradation (Kleinberg, 2015). A recent phase three clinical trial with 198 patients evaluating the effects of donepezil vs placebo in brain tumour survivors found that patients with the most severe initial cognitive impairments experienced the most pronounced benefits in regard to memory, attention and processing speed (Rapp et al., 2015) and health-related quality of life (Naughton et al., 2017). These benefits were, however, non-significantly
different between the treatment and placebo groups. As such, the current evidence regarding the pharmacological treatment of post-PFT cognitive and linguistic deficits, both in the acute and long-term recovery phases, cannot be considered sufficient or conclusive, and more systematic research is required.

**7.3.2 Behavioural interventions**

There is a variety of behavioural post-brain injury rehabilitation approaches, which are broadly classified as either restorative or compensatory. Cicerone (2005), based on a review of 47 cognitive rehabilitation studies, concluded that when it comes to language impairments, restorative methods are the most effective. These approaches are based on repetitive, systematic stimulation where patients are encouraged to build up lost skills over time. In contrast, compensatory strategies, based on the learning of alternative ways of performance, seem most effective for domains such as memory or functional skills (Brewer-Mixon & Cullum, 2013).

Only one identified study, by Zou et al. (2016), reports on the outcomes of language-related intervention in PFT survivors. The authors document the effects of a reading intervention in medulloblastoma survivors, administered while they were receiving radiation therapy. Two and a half years after the treatment, not only did the reading intervention group perform better on the reading tests, compared to standard-of-care patients, they also displayed a pattern of cortical activation on reading in-scanner fMRI tasks, which was
similar to the healthy control group. This suggests that there is scope for behavioural interventions that can make a positive impact on PFT patients’ language ability. Similar studies in the non-brain tumour population have demonstrated beneficial effects of the reading intervention on WM integrity. For example, Keller & Just (2009), in a sample of 47 poor readers, demonstrated that intensive reading skills tuition resulted in the increased FA within the left anterior centrum semiovale and an associated improvement in phonological decoding ability. In the patient sample of the present study reading ability was also found to be impaired, demonstrating scope for such an intervention. Similarly, this principle of repeated practice can be applied to other affected language functions such as comprehension, production and writing.

Younger children are most likely to benefit from timely behavioural rehabilitation as the language networks undergo active development during the first decade of life. For example, Szafirarlski et al. (2006), in a 5-year longitudinal fMRI study of language development, found that between the ages of 5 and 11 during semantic/lexical language processing healthy children increasingly recruit the left inferior, middle frontal, middle temporal and angular gyri, as well as the right lingual and inferior temporal gyri. At the same time, the contribution of the left posterior insula/extrastriate cortex, left superior frontal and right anterior cingulate gyri, and left thalamus gradually decrease during this period. Evidence for the high degree of neural plasticity in children also comes from clinical studies. Bates et al. (2001) compared language production in 38 children and 21 adults at least 6 months after a unilateral brain injury and found that, while all of the adults exhibited some language deficits, all of the children
performed within the norms for their respective ages. Although none of the patients in the study had a diagnosis of a brain tumour, these findings demonstrate that the prospect of language function recovery in childhood is much better than in adulthood. Thus, paediatric PFT patients with a high risk of developing long-term communication deficits must be identified early and provided with the necessary timely rehabilitation support. This will help to ensure that the optimal ‘window of opportunity’ for restoration of the affected functions, including language, is not missed.

7.4 Future research directions

During the three decades of the investigation of language dysfunction in PFT survivors, the objective has predominantly been to document the presence of linguistic deficits using behavioural assessment methods. Although such studies are able to detect overt functional impairments, the obvious limitation is the lack of insight into the associated neural bases. Combining behavioural assessment with neuroimaging is a more powerful way of achieving an understanding of how the overt deficits relate to the changes in the brain's structure and function.

In recent years, a number of studies have utilised structural imaging techniques in combination with behavioural assessment in order to demonstrate how an alteration in the white and grey matter in PFT survivors underpins changes in IQ, memory, attention, executive function etc. (e.g., Mulhern et al., 1999; Mabbott et al., 2006; Palmer et al., 2012). However, structural neuroimaging research concerned specifically with language processing in this group
of patients is still lacking. In the present study, we have demonstrated that language difficulties may be underpinned by a global and local decline in white matter quality. These preliminary findings demonstrate that there is scope for the application of more advanced structural imaging of the supra-tentorial white matter in relation to overt language impairments. For example, probabilistic tractography is used for more precise characterisation of the major white matter pathways, such as a description of their location and volume. This technique has previously been successfully applied to the investigation of the volumetric and microstructural changes in white matter underpinning general cognitive decline (Soelva et al., 2013, Law et al., 2015). Besides the changes in white matter, other structural imaging studies have reported a relationship between changes in the supra-tentorial grey matter and cognitive decline. For example, Moberget et al. (2015) examined the grey matter in childhood PFT survivors and found increased grey matter density in the bilateral cingulum, left orbitofrontal cortex and left hippocampus, which correlated with a decreased processing speed and executive function. The investigation of grey matter changes in relation to language processing difficulties is another important avenue for future research.

Functional MRI is another imaging modality that is currently under-utilised in cognitive and language research with PFT survivors. In the clinic, task-based language fMRI is predominantly used for pre-operative planning in patients with supra-tentorial tumours, yet the efficiency of the method is still being disputed and direct cortical stimulation remains the gold standard method (Giussani et al., 2010). In the
scientific research context, the technique has proven to be most successful in studies on the localisation of cortical activation during cognitive, motor and language task performance. As discussed in Chapters 1 and 4, the contribution of fMRI to language research is hard to overestimate and this method is currently the gold standard for the in-vivo study of language processing. The present thesis reported on the very first application of task-based language fMRI in PFT survivors and generated some important insights into cortical metabolic signatures of the covert articulation and semantic retrieval in this group of patients. Clearly, there is scope for much wider application of the fMRI method to the study of language processing in PFT survivors. Other language modalities could be effectively investigated such as language comprehension, auditory processing, articulatory planning etc. fMRI could also be used to investigate age and treatment-related metabolic signatures of language processing, considering that younger radiotherapy-treated children seem to be at an increased risk of developing linguistic deficits post-treatment compared to older children without a history of adjuvant treatment. One limitation of task-based language fMRI is that localisation of the activation areas is a lot less consistent compared to localisation of the motor function, with the achieved sensitivity being typically around 80% and the specificity 78% (Bizzi et al., 2008). Thus, larger scale studies are needed to reliably establish how the neural processing of language is altered in PFT survivors in the long-term recovery phase.

A combination of structural and functional MRI techniques is also being used increasingly to study the neural underpinnings of language. As an example, Saur et al. (2008), using a
combination of DTI and fMRI, were able to describe the dorsal and ventral language pathways in healthy subjects, associated with sound-to-motor and sound-to-meaning mapping. Using a similar methodology, the functioning and integrity of these pathways could be examined in PFT survivors in order to further disentangle the effect of the tumour and its treatment on the motoric and semantic aspects of language production.

Besides the common structural and MR imaging methods, neural tissue composition could be more closely examined using the magnetic resonance spectroscopy method (MRS), sometimes referred to as ‘in vivo biopsy’. This method allows for the examination of the local concentrations of different metabolites such as N-acetylaspartate (NAA), Choline (Cho), Creatine (Cr) and others that are known to be altered in neurodegenerative conditions (Castillo, Kwock, & Muckherji, 1996). For example, Rueckriegel, Driever, & Bruhn (2012), using H-1 MR spectroscopy, were able to demonstrate a reduced concentration of N-acetylaspartate (NAA) in WM and GM in medulloblastoma and astrocytoma survivors, and attributed this to the long-term effects of adjuvant radiotherapy and chemotherapy treatment. Future research using this method could reveal whether changes in chemical tissue composition underpin the functional deficits in language processing in PFT survivors.

Electric and magnetic encephalography (EEG and MEG) could also be effectively utilised to overcome the limitation of the low temporal resolution of fMRI. This is particularly important in cognitive and linguistic research where an understanding of the temporal relationship between the stimulus and its neural processing is vital. In one such study, Dockstader et al. (2013)
used MEG to investigate neural function during visuo-motor task performance in 15 malignant PFT survivors. They found delayed neural activation within the visual and motor cortices, muted motor response in the alpha and beta bandwidths, and potentiated visual and motor responses in the gamma bandwidth, indicating increased attentional effort, which was manifested in the compensatory neural activity. It is yet to be established whether such increased attentional demand is also true for language processing, and this question could be answered by future studies using MEG or EEG.

With growing acceptance that language function is supported by the distributed network of brain regions rather than specific structures, recent years have seen an increased application of network-based approaches for the analysis of neuroimaging data from language studies. One such increasingly popular approach is the study of the neural representations of language using graph theoretical tools (Bullmore & Sporns, 2009). The advantage of this method is that it permits a holistic view of the brain and an analysis of the interaction between the regions comprising the language network. Earlier applications of the network-based approach focused on resting state fMRI data. However, recently, this method has also been successfully applied to task-based fMRI. For example, Simonyan & Fuertinger (2015) mapped the speech production network in healthy subjects, and found that the inferior parietal lobe and the cerebellum, particularly Lobule IV, constituted the major hubs in this network. Although the network was bilaterally distributed, interregional connectivity was stronger within the left hemisphere,
consistent with the current understanding of left-lateralised hemispheric language dominance. Future studies of linguistic processing in PFT survivors, adopting this approach, could reveal whether the properties of the language network, comprising both the infra-tentorial and supra-tentorial regions, are altered in PFT survivors compared to healthy peers.

7.5 Conclusions

In summary, the understanding of the long-term sequelae of PFT sustained in childhood has advanced significantly over recent decades. In addition to the long-lasting cognitive and motor deficits, a growing body of research suggests that a large proportion of survivors suffer from long-lasting communication difficulties, which are evident from both measurement-based and self-report studies. The multi-modal investigation reported in this thesis offered the most comprehensive assessment of the language processing abilities of PFT survivors to date, highlighting impairments in a range of specific functions and a higher deficit prevalence compared to the general population. Moreover, the present work, for the first time, has demonstrated the neural signatures of the impaired language skills by applying functional and structural magnetic resonance imaging techniques, not previously utilised for this purpose in this patient group.

Future work in this field must take two primary directions. First of all, the need for rehabilitation of the communication skills should be recognised and behavioural intervention programmes should be developed in order to help survivors to
overcome these communication deficits for more successful educational progression and social re-integration. Secondly, more research into the neural correlates of the impaired communication abilities is necessary to verify and extend the present findings. The variety of the available neuroimaging techniques offer the means of addressing a number of relevant questions such as the changes in the strength, distribution and timing of the neural responses during linguistic processing, the associated structural and volumetric changes in the grey and white matter, the alterations in the chemical composition of the neural tissue, and the reorganisation of the whole-brain language networks. An in-depth investigation of the neural basis of impaired communication abilities would inform clinical decisions and rehabilitation practice, ultimately benefiting patients’ long-term functional prognosis.


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Bibliography


Bibliography


Appendix 1. Study protocol

LANGUAGE AND COMMUNICATION IN YOUNG ADULT SURVIVORS OF
CHILDHOOD POSTERIOR FOSSA TUMOURS

Draft 7.0
1.07.14

Short title: Language in childhood posterior fossa tumour survivors

NRES reference: 14/EM/0224

Study Sponsor: University of Nottingham

Sponsor reference: 14037

Funding Source: School of Psychology, University of Nottingham; Children’s Brain Tumour Research Centre, Nottingham

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Appendix 1 (continued). Study protocol

STUDY PERSONNEL AND CONTACT DETAILS

**Sponsor:**
University of Nottingham
Mr Paul Cartledge
Head of Research Grants and Contracts
Research and Graduate Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

**Chief investigator:**
Dr Nicola Pitchford
Associate Professor
Room C78
School of Psychology
University of Nottingham
University Park
Nottingham, NG7 2RD
Phone: 0115 95 15287
Fax: 0115 95 15324
Email: nicola.pitchford@nottingham.ac.uk

**Co-investigators:**
Dr Rob Dineen
Associate Professor
Room B1435 Queen's Medical Centre
Queen's Medical Centre
Nottingham
NG7 2UH
Phone: 0115 823 1173
Fax: 0115 823 1180
Email: rob.dineen@nottingham.ac.uk

Professor David Walker
Room EE 1833a Nottingham Children's Hospital
Queen's Medical Centre
Nottingham
NG7 2UH
Phone: 0115 823 0632/29
Fax: 0115 823 0622
Email: david.walker@nottingham.ac.uk
Appendix 1 (continued). Study protocol

Dr Denis Schluppeck
Lecturer
Room C63 School of Psychology
University Park
Nottingham
NG7 2RD
Tel: 0115 84 68580
Fax: 0115 95 15324
Email: denis.schluppeck@nottingham.ac.uk

Olha Hodgson
PhD Student
Room C72
School of Psychology
University of Nottingham
NG7 2RD
Tel: 01158466610
Email: lpxoh4@nottingham.ac.uk

Study Coordinating Centre: School of Psychology
University of Nottingham
University Park
Nottingham
NG7 2RD

Language and communication in young adult survivors of childhood posterior fossa tumours
Protocol Draft Version 7/1.07.2014

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### Appendix 1 (continued). Study protocol

#### SYNOPSIS

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<tr>
<th>Title</th>
<th>Language and communication in young adult survivors of childhood posterior fossa tumours</th>
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<tbody>
<tr>
<td>Acronym</td>
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<tr>
<td>Short title</td>
<td>Language in childhood posterior fossa tumour survivors</td>
</tr>
<tr>
<td>Chief Investigator</td>
<td>Dr Nicola Pitchford</td>
</tr>
<tr>
<td>Objectives</td>
<td>To assess the presence and severity of the language and communication impairments in childhood posterior fossa tumour (PFT) survivors during transition to adulthood, using standardised neuropsychological measures.</td>
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<td></td>
<td>To assess the discrepancies in the functioning of the key brain areas, implicated in language processing, between the PFT survivors and healthy controls, using functional magnetic resonance imaging.</td>
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<td></td>
<td>To assess the relationships between the language function and integrity of the cerebello-cerebral white matter tract, susceptible to damage during PFT resection, using diffusion-tensor imaging.</td>
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<tr>
<td>Study Configuration</td>
<td>Single centre observational study</td>
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<tr>
<td>Setting</td>
<td>Neuropsychological assessment of the patients undergoing routine follow-ups will take place at the Queen’s Medical Centre, Nottingham</td>
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<td></td>
<td>Neuropsychological assessment of the discharged patients and healthy controls will take place at the University of Nottingham, School of Psychology</td>
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<td></td>
<td>Neuroimaging assessment of all participants will take place at the Queen's Medical Centre, Nottingham</td>
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<td>Sample size estimate</td>
<td>Using a G*Power 3.9.1 software, it was determined that a sample size of 100 participants (50 patients and 50 healthy volunteers) would yield 93% power to detect a moderate effect size of 0.3, assuming significance level of 0.05.</td>
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Language and communication in young adult survivors of childhood posterior fossa tumours

Protocol Draft Version 7/1/2014

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### Appendix 1 (continued). Study protocol

<table>
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<tr>
<th>Number of participants</th>
<th>We are aiming to recruit 50 PFT patients treated at the Nottingham University Hospitals between 1992 and 2013</th>
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<tr>
<td></td>
<td>Further 50 healthy controls, matched by age and gender to the PFT survivors, will be recruited by means of involving patients’ friends or relatives to control for socio-economic background</td>
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<th>Eligibility criteria</th>
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<td>- posterior fossa tumour sustained before the age of 18 years,</td>
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<td>- male or female,</td>
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<td>- capacity to consent,</td>
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<td>- age between 16 years 0 months to 20 years 11 months at the time participation,</td>
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<td></td>
<td>- at least 12 months post-diagnosis at the time of participation in the study,</td>
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<td>- English as a primary language of schooling from at least the age of 11 years.</td>
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<th>Eligibility criteria</th>
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<td>- no history of cancer, neurological, psychiatric or developmental disorders,</td>
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<td>- male or female,</td>
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<td></td>
<td>- capacity to consent,</td>
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<td>- age between 16 years 0 months to 20 years 11 months at the time participation,</td>
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<td>- English as a primary language of schooling from at least the age of 11 years.</td>
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<tr>
<th>Description of interventions</th>
<th>Both patients and healthy controls will undergo same assessments, conducted over 2 separate visits</th>
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<td>Visit 1.</td>
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<td>Neuropsychological examination:</td>
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<td>- assessment of basic language functioning using CELF-V battery</td>
</tr>
<tr>
<td></td>
<td>- assessment of higher language functioning using CELF-V Metalinguistics battery</td>
</tr>
<tr>
<td></td>
<td>- assessment of non-verbal cognitive ability using Raven’s Progressive Matrices</td>
</tr>
<tr>
<td></td>
<td>- assessment of motor speech functioning using Frenchay</td>
</tr>
</tbody>
</table>

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### Appendix 1 (continued). Study protocol

<table>
<thead>
<tr>
<th>Dysarthria Profile</th>
<th>- Assessment of manual dexterity and visuo-motor coordination using Purdue Pegboard test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall duration with breaks - 3 hours 25 minutes</td>
</tr>
<tr>
<td><strong>Visit 2.</strong></td>
<td>- assessment of motor speech function and semantic fluency using custom-designed tasks</td>
</tr>
<tr>
<td></td>
<td>Magnetic resonance imaging:</td>
</tr>
<tr>
<td></td>
<td>- structural T1 weighted scan to provide anatomical reference for further analysis</td>
</tr>
<tr>
<td></td>
<td>- functional magnetic resonance imaging that will include 4 task-based scans</td>
</tr>
<tr>
<td></td>
<td>- diffusion weighted imaging scan</td>
</tr>
<tr>
<td></td>
<td>Overall time in the scanner - 47 minutes</td>
</tr>
<tr>
<td></td>
<td>Overall duration with breaks - 1 hour 37 minutes</td>
</tr>
</tbody>
</table>

#### Duration of study

Overall: 19 months

The recruitment and testing of participants will commence 1.09.2014 and will be finished by 31.03.2016

Each participant will be invited for assessment twice, with no more than 4 weeks between the visits

#### Outcome measures

**Primary:**
- CELF-V and CELF-V Metalinguistics core and index scores.

**Secondary:**
- Frenchay Dysarthria Profile rating
- Purdue Pegboard test score
- Automatic speech production and semantic fluency rates
- Percentage change in BOLD contrast in the cortical areas known to be implicated in language processing during the performance of the language tasks
- FA index in the regions of white matter localised to cerebello-cerebral white matter tract

#### Methods of analysis

Statistical analysis will be performed using SPSS software. Primary and secondary outcome measures will be analysed by comparing group means to investigate between-group differences in performance on CELF-V, CELF-V Metalinguistics, Frenchay Dysarthria Profile, Raven’s Progressive Matrices, Purdue Pegboard Test, as well as motor speech production and semantic fluency rates. Depending on the data distribution, parametric or non-parametric tests may be used.
Appendix 1 (continued). Study protocol

| Bivariate correlation analysis will be performed to establish the degree of association between the FA values, reflecting the cerebello-cerebral white matter tract integrity, and performance scores on CELF-V, CELF-V Metalinguistics, Frenchay Dysarthria Profile, Raven's Progressive Matrices, Purdue Pegboard Test, as well as motor speech production and semantic fluency rates. 

For the PFT group, a within-group regression analyses will be conducted to determine which clinical factors from the patient's history are predictive of language outcomes.

Group fMRI thresholded activation maps will be constructed for qualitative assessment of the cortical activation patterns during the performance of the fMRI tasks. |
Appendix 1 (continued). Study protocol

ABBREVIATIONS

AE    Adverse Event
BOLD  Blood Oxygenation Level Dependent contrast
CI    Chief Investigator overall
CELF-V Clinical Evaluation of Language Fundamentals, fifth edition
CRF   Case Report Form
DAP   Data Analysis Plan
DTI   Diffusion Tensor Imaging
DWI   Diffusion Weighted Imaging
FA    Fractional Anisotropy
FSL   FMRIB Software Library
fMRI  Functional magnetic resonance Imaging
GCP   Good Clinical Practice
ICF   Informed Consent Form
MRI   Magnetic Resonance Imaging
NHS   National Health Service
NUH   Nottingham University Hospitals
PI    Principal Investigator at a local centre
PIS   Participant Information Sheet
PFT   Posterior fossa tumour
QMC   Queens Medical Centre
REC   Research Ethics Committee
R&D   Research and Development department
UoN   University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

Posterior fossa tumours (PFTs) are the most common type of childhood tumours. With improvement in diagnosis and treatment in recent decades, around 85% of the patients survive for 5 years or longer after the treatment, many reaching adulthood (Lewis and Murdoch, 2013). This highlights the importance of monitoring and improving the quality of life and social integration of these patients.

There is strong evidence that long-term PFT survivors display a range of neurocognitive deficits. Recent systematic reviews of the literature highlight problems with global intelligence, executive function, working memory and attention (Wolfe et al, 2012; Robinson et al, 2013). Reduced quality of life and poor academic achievements have also been reported (Reimers et al, 2009; Odame et al, 2006). In addition, such patients often suffer from neurological and sensory deficits (Packer et al, 2003).

Linguistic and communication abilities are of vital importance for both social integration and educational progression. It is commonly reported that PFT survivors display slowed and scanning speech, in particular those experiencing complications such as Cerebellar Affective Syndrome or Cerebellar Mutism (De Smet et al, 2009). Evidence also suggests that higher language abilities may be impacted in PFT survivors (Aarsen et al, 2009; Docking et al, 2007). However, few studies to date have systematically examined underlying nature of these difficulties. Understanding impairments in specific linguistic domains can help in devising more effective rehabilitation therapies. In addition, understanding possible neural correlates of the language deficits can help in planning of the less damaging PFT treatment.

The present study aims to investigate the language and communication abilities in long-term PFT survivors during the transitional period in their lives - late teenage to early adulthood years. During this period important milestones are achieved such completion of secondary education and possibly moving to college or university, first employment and intimate relationships etc. It has been shown that peer communication and social activities are among the most important priorities for teenage cancer survivors (Farjou et al, 2013).

In this observational study we plan to conduct thorough assessment of language and speech using standardised neuropsychological measures and custom-designed behavioural tasks in order to detect specific domains of impairments. In addition, we will conduct magnetic resonance imaging (MRI) assessment, including functional imaging (fMRI) and diffusion tensor imaging (DTI). With fMRI, it will be possible to investigate patterns of cortical activation in the regions known to be implicated in linguistic processing during the performance of the language tasks. Using DTI, we will investigate the relationships between the language impairments and integrity of the cerebello-cerebral white matter tract, thought to be important for language and cognition, and susceptible to damage during the PFT resection (Morris et al, 2009; Soelva et al, 2013).
Appendix 1 (continued). Study protocol

The results of this study will inform clinical practice in several ways. First of all, by identifying domains of language and communication with the most marked deficits, our project will inform long-term rehabilitation practice. Secondly, identifying structural and functional neural correlates of impaired language will inform PFT treatment strategies aimed at achieving the best possible balance between improving survival and reducing functional impairments.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to investigate language functioning in long-term PFT survivors and neural correlates underlying any functional deficits.

PRIMARY OBJECTIVE

To measure language and communication proficiency in long-term PFT survivors. A comprehensive assessment of linguistic abilities will be conducted using clinically validated tests. The hypothesis to be tested is that PFT survivors display marked deficits in one or more language domains.

SECONDARY OBJECTIVES

To investigate the relationships between the symptoms of impaired language functioning, functional activation of the language-implicated cortical areas and structural integrity of the cerebello-cerebral white matter tract in the PFT and healthy control group.

To determine neurocognitive, clinical, neuroimaging and behavioural correlates of the language and communication deficits in PFT survivors.
Appendix 1 (continued). Study protocol

STUDY DESIGN

STUDY CONFIGURATION
This is a single-centre observational study. Young people who sustained posterior fossa tumours before the age of 18, currently between the ages of 16 and 21, at least 12 months post-diagnosis and received medical treatment at the Nottingham University Hospitals NHS trust, will be recruited for the study.

A control group will be recruited by means of encouraging participants to identify a friend or a relative of the same gender and similar age without the history of cancer, neurological and psychiatric diseases for best socio-economic matching. Where this is not possible, suitable healthy controls will be recruited by the Investigator (PhD student) from the local community.

All participants will complete all assessment measures once, and group differences in primary and secondary outcomes will be examined.

Primary endpoint

Primary endpoints are performance scores obtained from language assessment (CELF-V, CELF-V Metalinguistics and the Frenchay Dysarthria Profile).

Secondary endpoints

Secondary endpoints are
- performance scores obtained from the Purdue pegboard test,
- performance scores obtained from the motor speech production and semantic processing tasks,
- fMRI maximum intensity values in the language-implicated cortical areas during language tasks performance,
- FA coefficient values of the cerebello-cerebral white matter tract.

STUDY MANAGEMENT
The Chief Investigator, Dr Nicola Pitchford, has overall responsibility for the study and will oversee all study management.

The Investigator (PhD student Olha Hodgson), will be responsible for recruiting, testing, data management and analysis.
Appendix 1 (continued). Study protocol

The data custodian will be the Chief Investigator. The neuropsychological test forms will be stored on the premises of the UON Psychology department in a secure locked filing cabinet. Once the study is finished, all paper forms will be scanned and stored as electronic files, and the hard copies will be destroyed. Neuroimaging data will store on a password-protected UON server.

Other co-investigators will be Professor David Walker, Dr Rob Dineen and Dr Denis Schluppeck. Co-investigators will meet on a regular basis to oversee progress of the study.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Recruitment of the participants will commence once a favourable opinion from the Ethics Committee and relevant NHS R&D permissions has been granted.

The maximum duration of the study is 19 months. It is planned to begin enrolment 1.09.2014 and cease 31.03.2016.

Participants will be involved in the study from the time of recruitment until completion of both parts of the assessments (neuropsychological and imaging) which will take place on two separate days, with no more than 4 weeks between them. It is expected that participation in the study will not exceed 4 months.

Assessment sessions will be scheduled either in the morning or afternoon, with the duration of the Visit 1 being 3 hours 25 minutes, and Visit 2 - 1 hour and 37 minutes.

During neuropsychological assessment, regular breaks between the individual tests will be given. During imaging assessment, short breaks will be given between the scans, however, participants will remain in the scanner during such breaks, unless they request to come out or there is an emergency situation.

End of the Study

The study will end when the last recruited participant has completed all neuropsychological and imaging assessment procedures.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The study will take place on the University of Nottingham site. Permanently discharged PFT survivors and healthy controls will undergo neuropsychological assessment at the Psychology department where the CI and PhD student are based and suitable testing facilities available.
Appendix 1 (continued). Study protocol

PFT survivors due clinical follow-up appointments will be assessed at the QMC paediatric neuro-oncology unit. Research and clinical appointments will be synchronised in order to reduce time commitment for the patients, providing they give consent to participate in this research.

All participants will have neuroimaging assessment at the QMC where MRI scanner is located.

Participants in the clinical group will be selected from the NUH database of the patients treated for posterior fossa tumours since 1992. Nottingham University Hospitals NHS Trust has been chosen as a study setting because this project in jointly supported by the UON Department of Psychology and the Children’s Brain Tumour Research Centre (CBTRC), based at the Nottingham Queen’s Medical Centre (QMC).

The initial approach will be from a member of the patient’s usual care team (one of the oncologists). Information about the study will be on display in the relevant clinical areas.

Eligible PFT survivors will be contacted by letter which will inform them of all aspects pertaining to participation in the study and the contact details of the research team. This will also include a study information sheet regarding the neuropsychological and MRI assessment.

The recruitment letter will explain to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and may be used in the final analyses where appropriate (this will also be covered on clause 2 of the consent form and the withdrawal section of the participant information sheet).

Once the interested participants have contacted the research team, the Investigator (PhD student) will carry out an over-the-phone screening for any exclusion criteria. If none are identified and both sides agree to proceed, the potential participant will be encouraged to identify a friend or a family member of a similar age and same gender from their close social circle, in order to recruit a matched participant for the healthy control group. The procedure of initial contact and screening would be the same for healthy controls.

Where it is not possible to recruit a healthy control participant in this way, the Investigator will be responsible for recruiting best possible match from the local community. For this, advertising posters will be displayed in local colleges and sport centres.
Appendix 1 (continued). Study protocol

The investigator will make every effort to prevent unnecessary drop-out of participants by liaising with them regularly and making sure the discomfort of participation is kept to a minimum.

Eligibility criteria

Inclusion criteria

Patient group:
- PFT sustained before the age of 18 years,
- Age between 16 years 0 months and 20 years 11 months at the time of assessment
- Male or female
- Capacity to consent
- At least 12 months after the diagnosis at the time of assessment. In case of recurrent tumour, at least 12 months from the commencement of the latest treatment cycle
- English as a primary language of schooling from at least the age of 11 years.

Healthy controls group:
- Age between 16 years 0 months and 20 years 11 months at the time of assessment
- No history of cancer, neurological, psychiatric or developmental disorders
- Male or female
- Capacity to consent
- English as a primary language of schooling from at least the age of 11 years

Exclusion criteria

- Pregnancy (a pregnancy test will be provided to all female participants during the second visit before the MRI scan)
- Non-removable metal in the body (including body piercing or medical prostheses)
- Tattoo within 6 months prior to the MRI
- Claustrophobia
- A severe learning disability that prohibits capacity to consent
- Visual or hearing impairments unable to be corrected-to-normal
- Any other health or psychological issue precluding participation in the neuropsychological and imaging assessment

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Appendix 1 (continued). Study protocol

Expected duration of participant involvement

Participants will be involved in the study for no longer than four months from the point of recruitment to completion of the final assessment.

All participants will be invited for assessment twice, each visit lasting half of the day, either in the morning or in the afternoon.

On the first visit, neuropsychological assessment will be conducted, total duration no more than 3 hours 25 minutes.

On the second visit, behavioural and neuroimaging assessment will be performed, total duration no more than 1 hour 37 minutes.

Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the investigator.

Participants can withdraw at their own request at any stage and they can do so without having to disclose the reasons. The information sheets and consent forms will stipulate that, should participants decide to withdraw, the data already collected may still be used in the final analysis. It will also be stated that withdrawal from the study will not affect their future care.

The Investigator can make a decision to exclude a participant based on the health and safety reasons (e.g. pregnancy or previously undisclosed medical condition) or failure of the participant to adhere to the protocol requirements.

Where temporary discontinuation is possible, it will be preferred to the permanent discontinuation to achieve the best possible recruitment rates. However, re-recruitment will not be possible in the event of the consent withdrawal. All eligible NUH patients will be invited to participate in the study; therefore, replacement of the withdrawn participants would not be possible.

Informed consent

Informed consent will be sought from all participants directly. Participants will only be entered into the study if they have signed and dated the Informed Consent Form.

The Investigator (PhD student) will explain the details of the study and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider whether to participate or not. The Investigator will answer any questions concerning participation.
Appendix 1 (continued). Study protocol

One copy of the informed consent will be kept by the participant and one will be kept by the investigator.

Should there be any subsequent amendment to the final protocol, which might affect a participant’s involvement in the study, continuing consent will be obtained using an ethically approved amended Consent form which will be signed by the participant.

STUDY REGIMEN

From the clinical notes it will be established which eligible participants are permanently discharged and which are the out-patients due to undergo routine neuropsychological follow-up during the study period. Where possible, research and clinical appointments will be synchronised to reduce inconvenience for the participants.

Visit 1.
Participants deemed eligible will be invited to visit the Queen’s Medical Centre (if out-patients) or School of Psychology (if discharged), University of Nottingham, for the cognitive assessment at a mutually convenient time. At this stage they will also be asked to identify a friend or relative of a similar age and same gender to be a member the control group. Should a PFT patients and their chosen healthy control want to have their assessment carried out on the same day, this will be arranged for them.

Cognitive assessment will be administered by the PhD student, under supervision of the Chief Investigator, and will last up to 3 hours 25 minutes, including breaks. See Table 1 for a summary of the Visit 1 schedule.

At the end of the first visit, a second appointment for imaging assessment will be arranged, no later than 4 weeks after the first appointment.

Visit 2.
For imaging assessment, all participants will be invited to visit the Queen’s Medical Centre, where the MRI scanner is located. Female participants will be asked to take a pregnancy test (provided by the Investigator) to exclude the possibility of a pregnancy. In case of the positive test result, the MRI assessment will be cancelled but neuropsychological data collected so far may still be used in the final data analyses.

After completing MRI safety questionnaire, participants will be given two behavioural tasks assessing motor speech production and semantic fluency rates, lasting up to

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Appendix 1 (continued). Study protocol

10 minutes in total. The fMRI tasks will be explained and a short practice will be carried out. Following this, imaging will be performed by a radiographer with the Investigator present, total duration no more than 42 minutes. See Table 2 for a summary of the Visit 2 schedule.

Table 1. Visit 1 schedule

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Purpose</th>
<th>Time required (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting up</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Clinical Evaluation of Language Fundamentals battery, fifth</td>
<td>To measure core language skills</td>
<td>45 minutes</td>
</tr>
<tr>
<td>edition (CELF-V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Clinical Evaluation of Language Fundamentals Metalinguistics,</td>
<td>To measure higher language skills</td>
<td>45 minutes</td>
</tr>
<tr>
<td>fifth edition (CELF-V Metalinguistics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Raven's Progressive Matrices</td>
<td>To measure non-verbal cognitive abilities</td>
<td>40 minutes</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>The Frenchay Dysarthria Profile (RDT)</td>
<td>To measure motor speech functioning</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Break</td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td>Purdue pegboard tests</td>
<td>To measure manual dexterity and visuo-motor</td>
<td>10 minutes</td>
</tr>
<tr>
<td></td>
<td>coordination</td>
<td></td>
</tr>
<tr>
<td>Total neuropsychological assessment time</td>
<td></td>
<td>2 hours 40 minutes</td>
</tr>
<tr>
<td>Total visit time</td>
<td></td>
<td>3 hours 25 minutes</td>
</tr>
</tbody>
</table>
### Appendix 1 (continued). Study protocol

**Table 2. Visit 2 schedule**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Purpose/Outcome of interest</th>
<th>Time required (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test (for female participants)</td>
<td>To exclude the possibility of pregnancy</td>
<td>10 minutes</td>
</tr>
<tr>
<td>fMRI safety questionnaire</td>
<td>To measure rate of the motor speech production with minimal semantic load per unit of time</td>
<td>10 minutes</td>
</tr>
<tr>
<td><strong>Behavioural task 1</strong></td>
<td><strong>Motor speech production. Participants will be asked to recite aloud highly rehearsed sequence of words (months of the year)</strong></td>
<td><strong>5 minutes</strong></td>
</tr>
<tr>
<td><strong>Behavioural task 2</strong></td>
<td><strong>Semantic processing. Participants will be shown pictures of objects and will be asked to generate related verbs (i.e. ball – kick)</strong></td>
<td><strong>5 minutes</strong></td>
</tr>
<tr>
<td>fMRI task practice</td>
<td>To ensure participants understand the language tasks they will be performing in the scanner</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Break/ Setting up participant in the scanner</td>
<td></td>
<td>15 minutes</td>
</tr>
<tr>
<td>Localiser scan</td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td>T1-weighted structural scan</td>
<td>To provide anatomical reference for the MRI data analysis</td>
<td>10 minutes</td>
</tr>
<tr>
<td><strong>fMRI scan 1.</strong></td>
<td><strong>Alternating blocks of rest, automatic speech production (silently reciting months of the year) and semantic processing (silently generating names of the months in response to pictures of the nature scenes) tasks.</strong></td>
<td><strong>5 minutes 30 seconds</strong></td>
</tr>
<tr>
<td>fMRI scan 2.</td>
<td>Same as scan 1</td>
<td>5 minutes 30 seconds</td>
</tr>
<tr>
<td>DWI scan</td>
<td>To provide diffusion map of the white matter</td>
<td>10 minutes</td>
</tr>
<tr>
<td><strong>fMRI scan 3.</strong></td>
<td>Same as scan 1.</td>
<td>5 minutes 30 seconds</td>
</tr>
</tbody>
</table>

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Appendix 1 (continued). Study protocol

<table>
<thead>
<tr>
<th>Study protocol details</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as scan 1</td>
<td></td>
</tr>
<tr>
<td>fMRI scan 4. Same as scan 1</td>
<td>Same as scan 1.</td>
</tr>
<tr>
<td>Total behavioural assessment time</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Total scanning time</td>
<td>47 minutes</td>
</tr>
<tr>
<td>Total visit time</td>
<td>1 hour 37 minutes for females 1 hour 27 minutes for males</td>
</tr>
</tbody>
</table>

The option to withdraw from any tasks will be emphasised throughout and awareness of the limits of each individual participant will be a priority. At the end of the second visit, each participant will be presented with a £50 Amazon voucher, regardless of the level of completion of the study assessment.

Following the completion of data analysis, participants will be sent a newsletter that summarises the main findings from the study. Results of individual test scores will not be divulged to participants or their guardians as the tests are not diagnostic.

Compliance

Participants’ compliance to the study protocol is vital for ensuring high quality of the collected data.

During neuropsychological and behavioural assessment, it will be emphasised that participants should strive to perform to their optimal ability. Where participants demonstrate obvious non-compliance, the testing will be terminated and data removed from the analysis.

During fMRI assessment, it will be reiterated that participants should remain still in the scanner and strive to perform to their optimal ability on the fMRI tasks. The quality of the data during pre-processing will serve as an indicator of compliance in this case. If researchers identify significant movement artefacts or total absence of BOLD activity relevant to the task, such data will be removed from the analysis.

Criteria for terminating the study

The study may be terminated early if there is overwhelming evidence of inefficacy, major safety concerns or issues with study conduct (e.g. poor recruitment, loss of resources).

Collected research data will be archived, according to UON standard procedures.
Appendix 1 (continued). Study protocol

ANALYSES

Methods

Data analysis will be conducted by Olha Hodgson, the PhD student under the supervision of the CI, Dr Nicola Pitchford.

CELF-V, CELF-V Metalinguistics, Frenchay Dysarthria Profile, Raven's Progressive Matrices and Purdue Pegboard test will be evaluated and scored according to the instruction manuals. Resulting data including core scores, index scores and individual test scores will be stored in an Excel Master Data file.

Motor speech production and semantic processing tasks will be scored according to the rate of word generation per minute (e.g. a score of 30 on a motor speech production task will mean that the participant managed to generate 30 month names in correct order in 1 minute). Resulting scores will be stored in the Excel Master data file.

MRI data will be analysed using FMRIB Software Library (FSL). The FSL FEAT tool will be used for the first-level analysis, and the FSL FLAME tool for the higher-level analysis of the functional MRI data. A region of interest (ROI) approach will be adopted and maximum intensity values from the specified ROIs will be recorded for each participant and stored in the Excel Master data file. Thresholded activation maps will also be produced using FSL for visualisation of individual and group cortical activation.

FSL FDT tool will be used for pre-processing of raw diffusion-weighted imaging data and TBSS tool will be used for the voxel-wise statistical analysis of the fractional anisotropy (FA) data. The ROI approach will be adopted and FA values for the specified ROIs will be recorded for each participant and stored in the Excel Master data file. FA maps will be produced for visualisation of the white matter tracts.

In addition, available clinical data for each patient will be added to the Master Data file, including tumour type, tumour location, age at diagnosis, duration since diagnosis at the time of assessment, treatment type, surgical approach, history of mutism and previous neuropsychological assessment results etc.

Statistical analyses will be performed using SPSS software. Primary and secondary outcome measures will be analysed by comparing group means to investigate between-group differences in performance on CELF-V, CELF-V Metalinguistics, Robertson Dysarthria Profile, Purdue Pegboard Test, Raven's Progressive Matrices, as well as motor speech production and semantic processing tasks. It is
Appendix 1 (continued). Study protocol

hypothesised that the PFT group will display marked deficits on one or more of these measures.

Bivariate correlation analyses will be performed to establish the degree of association between the FA values, reflecting the degree of cerebello-cerebral white matter tract integrity, and performance scores on CELF-V, CELF-V Metalinguistics, Robertson Dysarthria Profile, Purdue Pegboard Test, as well as motor speech production and semantic processing tasks. It is hypothesised that lower FA will correlate with lower scores on all measures.

Group fMRI thresholded activation maps will be constructed for qualitative assessment of the cortical activation patterns during the performance of the fMRI semantic/phonological fluency and language comprehension tasks. It is hypothesised that the PFT group will display differences in activation of the language-implicated ROIs, compared to the healthy control group.

In addition, for the PFT group, a within-group multiple regression analyses will be conducted to determine which clinical factors from the patient's history are predictive of language outcomes.

Analysis will be conducted on the UoN premises, using the university computers and with regular backing-up of the data to the UoN servers. All participant data will be anonymised to maintain confidentiality.

Sample size and justification

Currently there are 50 surviving patients on the NUH database who satisfied the inclusion criteria for the study.

Using a G*Power 3.9.1 software (Foul et al, 2007), it was determined that a sample size of 100 participants (50 patients and 50 healthy controls) would yield 93% power to detect a moderate effect size of 0.3, assuming significance level of 0.05.

In the event of a 50% recruitment rate, the remaining sample of 50 participants (25 patients and 25 healthy controls) would yield 70% power to detect a moderate effect size of 0.3, assuming significance level of 0.05.

Procedures for missing, unused or spurious data

We plan to minimise the missing data. During the neuropsychological assessment (Visit 1), the aim will be to administer all assessment tests in full. To account for fatigue effects, 10-minutes breaks have been included between every battery. However, should a participant's performance fall below the level necessary for the
Appendix 1 (continued). Study protocol

test completion, discontinuation rules will be applied in accordance with each battery's instruction manual. In this event, missing data points will be replaced before analysis with a value that reflects the mean and variance of the group. This will allow retention of all cases without spuriously changing the magnitude of effects. The same rule will apply for performance on language tasks during Visit 2.

MRI structural scans are unlikely to result in missing data as there are no performance demands for participants. fMRI task data is also unlikely to result in missing data as the analysis averages many data points. Although averaged data can be noisy and some data points could be rejected due to movement artefacts, the design and lengths of the fMRI tasks permit acquisition of sufficient amount of data to reject unusable data without affecting the quality of the results. In addition, to prevent movement artefacts, participants will be instructed to remain still in the scanner and given short breaks between the scans to prevent discomfort.

Statistical analysis of the quantity and type of missing data between groups will be conducted to ensure missing data is not systematically biasing comparisons of study groups, which may affect interpretations.

ADVERSE EVENTS

Although occurrence of the adverse events as a result of administering neuropsychological tests and language tasks is not expected, participants will be asked to contact the research team immediately, should any adverse events occur. All adverse events will be recorded and monitored carefully until resolution, or until it has been shown that the study assessment is not the cause.

In the event that an unsuspected abnormality is identified on the scan by one of the researchers, the images will be reviewed by a qualified consultant neuroradiologist working within the Division of Radiological and Imaging Sciences. If the suspicion of a significant abnormality is confirmed, the neuroradiologist involved will contact participant's GP and advise on appropriate measures which will need to be taken in light of the findings, these may include performing further scans or advising on referral to an appropriate hospital-based specialist. The finding of a significant unexpected abnormality may have benefits in that it may be possible to offer treatments earlier than would otherwise have been possible.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research
Appendix 1 (continued). Study protocol

Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative will both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A third copy will be filed in the participant’s medical notes and a signed and dated note made in the notes that informed consent was obtained for the study.

The decision regarding involvement in the study is entirely voluntary. The investigator or their nominee will emphasize to the participants that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator will follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).
Appendix 1 (continued). Study protocol

RECORDS

Case Report Forms

Each participant will be assigned a single study identity code number for use on CRFs, other study documents and electronic database. The identity code will be made up of initials and a date of birth to prevent misidentification of participants (for example, OH160582).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant’s name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required. CRFs shall be restricted to those personnel approved by the Chief Investigator and recorded as such in the study records.

All paper forms will be filled using black ballpoint pen. Errors will be lined out but not obliterated by using correction fluid, and the corrections will be inserted, initialled and dated. The PhD student and the CI will be authorised to make entries.

Hard copies of the neuropsychological test forms and consent forms will be kept at UON Psychology Department premises and stored in a secure locked filing cabinet in PhD student’s office. After the completion of the study they will be scanned and retained as electronic copies together with the Master Data File. The Electronic Master Data File containing imaging data, Excel database and statistical analysis output files will be password protected and frequently backed up to the UON server.

The Chief Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the Investigator’s site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its...
Appendix 1 (continued). Study protocol

own source data. Only study staff will have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents will made be available at all times for review by the Chief Investigator, Sponsor’s designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study’s participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked filing cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant’s medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability
Appendix 1 (continued). Study protocol

insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct will be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Monitoring of study data will include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The CI, Dr Nicola Pitchford, as the student's academic supervisor, or where required, a nominated designee of the Sponsor, will carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
Appendix 1 (continued). Study protocol

The Study Master File held by the Chief Investigator on behalf of the Sponsor will be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant’s medical team and all appropriate medical personnel responsible for the participant’s welfare.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Following the completion of the study, findings will be written and contribute to the doctoral thesis of Olha Hodgson. Findings will be also presented at local and international academic conferences (e.g. International Society of Paediatric Neuro-Oncology, British Neuro-Oncology Society). Based on the findings, articles will be submitted for publication to peer-reviewed scientific journals (e.g. British Journal of Neuro-Oncology, Paediatric Neurology). Individual participants will not be identified in any publications.
Appendix 1 (continued). Study protocol

USER AND PUBLIC INVOLVEMENT

Similar assessments have been developed and performed by members of the study team, and have received positive feedback from both healthy population and brain tumour patients.

The research team are currently working with the children’s cancer charity Clic Sargent whose service users have agreed to review the study information sheets, consent forms and research protocol in order give their opinion on how participant-friendly is the proposed research.

STUDY FINANCES

Funding source
This study is funded by a PhD studentship to Olha Hodgson, for which half of the funding comes from the School of Psychology, University of Nottingham, and half from the Children’s Brain Tumour Research Centre (CBTRC), Nottingham.

Participant stipends and payments
Each participant will be offered a £50 Amazon voucher as a reward for supporting this research.
Appendix 1 (continued). Study protocol

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Dr Nicola Pitchford

Signature: ____________________________

Date: 14.05.2014

Co-investigator: Olha Hodgson

Signature: ____________________________

Date: 14.05.2014
Appendix 1 (continued). Study protocol

REFERENCES


This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by others persons without prior written authorisation from the University of Nottingham
Appendix 1 (continued). Study protocol


Appendix 2. NHS Research Ethics Committee Approval

16 July 2014

Dr Nicola Pitchford
School of Psychology
University Park
University of Nottingham
NG7 2RD

Dear Dr Pitchford,

Study title: Language and communication in young adult survivors of childhood posterior fossa tumours

REC reference: 14/EM/1017
Protocol number: 14037
IRAS project ID: 144823

Thank you for your letter of 14 July 2014, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Rebecca Morledge, NRESCommittee.EastMidlands-Northampton@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.
Appendix 2 (continued). NHS Research Ethics Committee approval

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk).

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
Appendix 2 (continued). NHS Research Ethics Committee approval

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.
Appendix 2 (continued). NHS Research Ethics Committee approval

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/1017 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project.

Yours sincerely,

Mr Ken Willis
Chair

Email: NRESCommittee.EastMidlands-Northampton@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mr Paul Cartledge
Charlotte Davies, Research and Innovation
Appendix 3. Nottingham University Hospitals Research and Innovation approval

Dr Nicola Pitchford / Mrs Olha Hodgson
University of Nottingham
School of Psychology
University Park
Nottingham
NG7 2RD

Dear Dr Nicola Pitchford / Mrs Olha Hodgson

Re: 14CS024
CSP
REC 14/EM/1017

Language in childhood posterior fossa tumour survivors

The R&I Department has reviewed the following documents and NHS permission for the above research has been granted on the basis described in the application form, protocol, and supporting documentation. The documents reviewed were:

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Appendix 3 (continued). Nottingham University Hospitals Research and Innovation approval

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Your study now has NHS permission, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

The Principal Investigator is responsible for

1. Compliance with all relevant laws, regulations and codes of practice applicable to the trial including but not limited to, the UK Clinical Trials Regulations, Medicines for Human Use (Clinical Trial) Regulations 2004, principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ (2013 version), the Human Rights Act 1998, the Data Protection Act 1998 the Medicines Act 1968, the NHS Research Governance Framework for Health and Social Care (version 2 April 2005). Should any of these be revised and reissued this will apply. Copies of the up-to-date regulations are available from the R&I Office or via the R&I website [http://nuhrii.org](http://nuhrii.org)

2. Submission of study amendments to the Ethics committee and MHRA in accordance with the IRAS guidlines. Amendments and information with regards to changes in study status must be sent to R&I, (this includes changes to the local study team). Within 35 days from the receipt of a valid amendment submission, the R&I department will inform you if the amendment may not be implemented locally. If no objections are raised NHS permission is valid and the amendment may be implemented.
Appendix 3 (continued). Nottingham University Hospitals Research and Innovation approval

When submitting documents for studies adopted into the NIHR portfolio please send the information to the Clinical Research Network for the East Midlands (uhc-tr.CRNEastMidlandsCSP@nhs.net) When submitting documents for all other studies please use the email address rdamend@nuh.nhs.uk

3. Ensuring all study personnel, not employed by the Nottingham University Hospitals NHS Trust hold either honorary contracts/letters of access with this Trust, before they have access to any patients or staff, their data, tissue or organs or any NUH facilities.

4. In accordance with the Department of Health’s Plan for Growth, for initialising and delivering research within the NHS the first patient, first visit should occur 70 days from receipt of a valid submission in R&I. This applies to all where:
   - The sponsor is a commercial partner
   - NUH holds a funding contract with the National Institute for Health Research (NIHR)
   - The research is classed as a "clinical trial" on the IRAS filter page.

4. The research team via an identified individual is expected to collaborate with the department of R&I and the Clinical Research Network for the East Midlands in reporting recruitment data using Documaps and the NIHR National Tracker system.

5. For GTAC-approved studies, the NHS permission should be forwarded to GTAC via the sponsor. GTAC should then issue a site authorisation letter which must be received by each site prior to recruitment commencing. A copy of this letter must be forwarded to R&I.

6. Comply with requests from NUH R&I to allow monitoring of research to comply with the Research Governance framework.

7. Record all types of adverse events (including Suspected Unexpected Serious Adverse Drug Reaction - SUSARs) in the patient medical records and study documentation and report to the sponsor as required by the protocol.

8. Report any Serious Breach of the UK Clinical Trial regulations in connection with the trial or Serious Breach of the protocol, immediately after becoming aware of the breach to the study sponsor.

For NUH sponsored studies only, the Chief Investigator is responsible for:

i. All duties as detailed in the "Clinical Trial Delegation of Sponsorship responsibilities to Chief Investigator" agreement.

ii. Contacting the sponsor for review of all amendment documentation prior to submission to the HRA and MHRA. Please note that according to HRA and MHRA regulations, all submissions of amendments need to be signed by the authorised sponsor’s representative. All relevant documentation should be emailed to rdamend@nuh.nhs.uk.

iii. Send copies of the completed Annual Progress Reports, Development Safety Update Reports, and End of Study report required by the Ethics Committee and the MHRA (if appropriate) to the sponsor.
Appendix 3 (continued). Nottingham University Hospitals Research and Innovation approval

(researchsponsor@nuh.nhs.uk)

iv. Notify NUH R&I of all SAEs by completing and sending the "Serious Adverse Event reporting form" to R&I (only via fax, e-mail or by hand), within 24hrs of becoming aware of the event. Further guidance can be found in the R&I Adverse Event SOP (SOP-RES-019)

v. Reporting any Serious Breach of the UK Clinical Trial regulations in connection with the trial or Serious Breach of the protocol, immediately after becoming aware of the breach to NUH R&I as sponsor. Further guidance can be found in the R&I Non Compliance and Serious Breach Reporting SOP (SOP-RES-017)

This approval letter constitutes a favourable Site Specific Assessment (SSA) for this site.

Please note that the R&I department maintains a database containing study related information, and personal information about individual investigators e.g. name, address, contact details etc. This information will be managed according to the principles established in the Data Protection Act.

Yours sincerely,

[Signature]

Dr Brian Thomson / Dr Maria Koufali
Director of Research and Innovation / Deputy Director Research and Innovation
Appendix 4. Patient Information Sheet

Patient Information Sheet

Title of Study: Language and communication in young adult survivors of childhood posterior fossa tumours

Names of Researchers: Dr Nicola Pitchford, Professor David Walker, Dr Rob Dineen, Dr Denis Schluppeck, Miss Olha Hodgson

We would like to invite you to take part in our research study. Before you decide whether to take part we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

Many more people survive brain cancer than ever before. However, common treatment methods have certain side-effects. For example, it is known that some patients experience speech and language problems after treatment. It is important to understand which aspects of language are mostly affected, so treatment and rehabilitation can be planned more carefully in the future.

The purpose of this study is to compare language functioning in young people who were treated for brain tumours in the past, and their peers who have no history of cancer. This will be
Appendix 4 (continued). Patient Information Sheet

done by testing language skills using various tasks. In addition, safe and painless MRI scans will be performed to compare brain functioning in these two groups.

Why have I been invited?
You are being invited to take part because you had a brain tumour in the past and are currently between the ages of 16 and 21. We are inviting 50 participants like you to take part, and 50 volunteers who have not had cancer in the past.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?
You will be asked to attend the research facility twice, each time for half of the day (either in the morning or in the afternoon). It is best that the visits happen as close to each other as possible, with maximum of four weeks in between.

On a first visit, you will have the study explained to you by a member of the research team, and you will be asked to sign the consent form. Then the researcher will complete a series of
tests with you with short breaks in between. The total duration of your first visit will be no more than 3.5 hours.

On a **second visit**, you will first complete a short questionnaire to make sure you are safe to undergo an MRI scan (i.e. don't have fear of closed spaces or have any metal in your body).

If you are a female, you will be asked to take a pregnancy test. It is not recommended to have MRI during the first trimester of the pregnancy as effects of the magnetic field on the foetus are not known. You will not be scanned if the test is positive.

If it is safe to proceed, the researcher will ask you to complete two short language tasks (no more than 5 minutes each). After this, you will have the MRI scan. This involves lying in the MRI scanner for a period of around 50 minutes while we acquire the images. Sometimes you will be asked to simply lay still, and sometimes you will be shown pictures on the screen and asked to think about associated words.

While in the scanner, you will have protective earplugs or earphones on as MRI scanners can be quite noisy. Most people undergo MRI scanning without any difficulty, but if you need to, you will be able to contact the MRI technician at any time during the scan via an intercom or with an emergency buzzer. Following the MRI scan, your participation in the study is complete. There are no blood tests and there is no requirement to take any medications. The total duration of your second visit should not exceed 2 hours

**Expenses and payments**

You will be offered a £50 Amazon voucher at the end of your participation.
Appendix 4 (continued). Patient Information Sheet

What are the possible disadvantages and risks of taking part?

Provided you do not have condition which prevents you from having an MRI scan, there are no risks associated with this study. You will be screened for conditions preventing you from having MRI before the scan.

The MRI scanner is a relatively enclosed space and occasionally participants can feel claustrophobic. During the scan you will be able to speak to the researchers performing the scan. If you would like to come out of the scanner at any time, you can request this. If you know that you are claustrophobic, we would advise against you participating.

In the unlikely event that an unsuspected abnormality is identified on the scan, the images will be reviewed by a qualified consultant neuroradiologist. If needed, the neuroradiologist involved will contact your GP and advise on appropriate measures. These may include performing further scans or advising on referral to an appropriate hospital-based specialist. The finding of a significant unexpected abnormality may have benefits in that it may be possible to offer treatments earlier than would otherwise have been possible.

What are the possible benefits of taking part?

There are no direct benefits for the individual in taking part in the study. However, the study aims to improve our understanding of what language difficulties sometimes occur in people who are treated for brain tumours, and whether this is due to structural changes in the brain. We hope this information will be useful in the future for helping to develop effective prevention and rehabilitation for these problems.

What happens when the research study stops?

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Appendix 4 (continued). Patient Information Sheet

When the study is finished, all research data will be archived and stored for 7 years in accordance with the University of Nottingham regulations. After this, it will be destroyed securely.

What if there is a problem?

In case you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet.

If this route fails to achieve a satisfactory resolution and you still wish to complain about any aspect of this study, the normal National Health Service complaints mechanisms may be available to you. The Patient Advice and Liaison Service (PALS) can be contacted for further assistance at QMC by calling 0800 1830204.

Will my participation in the study be kept confidential?

With your permission, we will inform your GP about you agreeing to participate in this study. However, all information which is collected about you during the course of the research is strictly confidential and will be kept on a password protected database. Any information about you will have your name and address removed (anonymised). Your personal details will not be passed onto any third parties. The University of Nottingham procedures for handling, processing, storage and destruction of their data meet the requirements of the Data Protection Act 1998.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised
Appendix 4 (continued). Patient Information Sheet

persons to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and will do their best to meet this duty.

What will happen if I don’t want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reasons, your legal rights will not be affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

If you agree to take part in this study, with your permission we will write a short letter to your GP informing them of your decision with a brief description of the assessments we use. We will explain that the research data cannot be treated as diagnostic and individual results cannot be released to the GP. We will enclose this information sheet so your GP can see exactly what you have been told.

Please note, your GP will be contacted in the unlikely event if an unsuspected abnormality is identified on the scan by one of the researchers, and after it has been reviewed by a qualified consultant neuroradiologist.

What will happen to the results of the research study?

It is hoped that the results of the study will be published in scientific journal and presented at the international scientific meetings. You will not be identified in any report or publication.
Appendix 4 (continued). Patient Information Sheet

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is jointly funded by the School of Psychology and the Children's Brain Tumour Research Centre.

The study will contribute towards the doctoral thesis of Miss Olha Hodgson, who is a PhD student at the School of Psychology. She will be responsible for data collection and analysis in this study.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Northampton Research Ethics Committee.

Further information and contact details
If you would like to discuss the study further or would like more information, please feel free to contact the research team:

Chief Investigator
Dr Nicola Pitchford
Associate Professor
C78 School of Psychology
University of Nottingham
University Park
Nottingham, NG7 2RD
Phone: 0115 95 15287
Fax: 0115 95 15324

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Email: Nicola.Pitchford@nottingham.ac.uk

**PhD student responsible for data collection and analysis**

Olha Hodgson  
B76 School of Psychology  
University of Nottingham  
NG7 2RD  
Tel: 01158468188  
Email: lpoh4@nottingham.ac.uk
Appendix 5. Patient Consent Form

CONSENT FORM
(Patient)

Title of Study: Language and communication in young adult survivors of childhood posterior fossa tumours

REC ref: 14/EM/1017

Names of Researchers: Dr Nicola Pitchford, Professor David Walker, Dr Rob Dineen, Dr Denis Schuppeck, Miss Olha Hodgson

Name of Participant:  

Please initial box

1. I confirm that I have read and understood the information sheet version number ……….dated……………………………… for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw, then the information collected so far cannot be erased and that this information may still be used in the project analysis.

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to me taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

4. I give permission for individuals from the University of Nottingham to inform my GP about my participation in this study. I understand that my performance data will not be treated as diagnostic and will not be disclosed to any third parties, including GP.
   My GP contact details are:
   Name
   Address
   Telephone number

5. In the event that an unexpected finding is identified on my brain scan, I agree to my GP being informed.

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Appendix 5 (continued). Patient Consent Form

6. Female participants only – I agree to take a pregnancy test before the MRI scan. I understand that in the event of a positive pregnancy test, I will not be permitted to have the MRI scan. However, the neuropsychological data gathered so far may still be used in the final data analyses.

7. I agree to take part in the above study.

Name of Participant ___________________________

Date ___________________________

Signature ___________________________

Name of Person taking consent ___________________________

Date ___________________________

Signature ___________________________

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes
Appendix 6. fMRI task script

#!/usr/bin/env python2
# -*- coding: utf-8 -*-

This experiment was created using PsychoPy2 Experiment Builder
(v1.81.03), July 22, 2015, at 16:44
If you publish work using this script please cite the relevant PsychoPy
publications

of Neuroscience Methods, 162(1-2), 8-13.

from __future__ import division  # so that 1/3=0.333 instead of 1/3=0
from psychopy import visual, core, data, event, logging, sound, gui
from psychopy.constants import * # things like STARTED, FINISHED
import numpy as np # whole numpy lib is available, prepend 'np.'
from numpy import sin, cos, tan, log, log10, pi, average, sqrt, std,
deg2rad, rad2deg, linspace, asarray
from numpy.random import random, randint, normal, shuffle
import os # handy system and path functions

# Ensure that relative paths start from the same directory as this script
__thisDir = os.path.dirname(os.path.abspath(__file__))
__thisDir = os.chdir(__thisDir)

# Store info about the experiment session
expName = 'Loop'  # from the Builder filename that created this script
expInfo = {u'session': u'001', u'participant': u''}
dlg = gui.DlgFromDict(dictionary=expInfo, title=expName)
if dlg.OK == False: core.quit()  # user pressed cancel
expInfo['date'] = data.getDateStr()  # add a simple timestamp
expInfo['expName'] = expName

# Data file name stem = absolute path + name; later add .psyexp, .csv,
# .log, etc
filename = __thisDir + os.sep + 'data/%s_%s_%s'
%(expInfo['participant'], expName, expInfo['date'])

# An ExperimentHandler isn't essential but helps with data saving
thisExp = data.ExperimentHandler(name=expName, version='',
extraInfo=expInfo, runtimeInfo=None,
originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.psyexp',
savePickle=True, saveWideText=True,
Appendix 6 (continued). fMRI task script

```python
dataFileName = filename
# save a log file for detail verbose info
logFile = logging.LogFile(filename+'.log', level=logging.DEBUG)
logging.console.setLevel(logging.WARN) # this outputs to the screen, not a file
endExpNow = False # flag for 'escape' or other condition => quit the exp

# Start Code - component code to be run before the window creation

# Setup the Window
win = visual.Window(size=(1280, 960), fullscr=True, screen=0,
                   allowGUI=False, allowStencil=False,
                   monitor='testMonitor', color=[0,0,0], colorSpace='rgb',
                   blendMode='avg', useFBO=True,
                   )
# store frame rate of monitor if we can measure it successfully
expInfo['frameRate'] = win.getActualFrameRate()
if expInfo['frameRate'] != None:
    frameDur = 1.0/round(expInfo['frameRate'])
else:
    frameDur = 1.0/60.0 # couldn't get a reliable measure so guess

# Initialize components for Routine "Instr4"
Instr4Clock = core.Clock()
text_4 = visual.TextStim(win=win, ori=0, name='text_4',
                         text='Are you ready? \nPress any button to start the experiment',
                         font='Arial',
                         pos=[0, 0], height=0.1, wrapWidth=None,
                         color='white', colorSpace='rgb', opacity=1,
                         depth=0.0)

# Initialize components for Routine "waitForTrigger"
waitForTriggerClock = core.Clock()
grating = visual.GratingStim(win=win, name='grating', units='deg',
                           tex='sin', mask='circle',
                           ori=0, pos=[0, 0], size=[0.5, 0.5], sf=0, phase=0.0,
                           color=[0.7, 0.7], colorSpace='rgb', opacity=1,
                           texRes=128, interpolate=True, depth=0.0)

# Initialize components for Routine "selectCondition"
selectConditionClock = core.Clock()

# Initialize components for Routine "trial"
trialClock = core.Clock()
Stim = visual.ImageStim(win=win, name='Stim', units='deg',
```
Appendix 6 (continued). fMRI task script

```python
image='sin', mask=None,
ori=0, pos=[0, 0], size=[10, 10],
color=[1,1,1], colorSpace='rgb', opacity=1,
flipHoriz=False, flipVert=False,
texRes=128, interpolate=True, depth=0.0
grating_3 = visual.GratingStim(win=win, name='grating_3', units='deg',
tex='sin', mask='circle',
ori=0, pos=[0, 0], size=[0.5, 0.5], sf=0, phase=0.0,
color=[1,1,1], colorSpace='rgb', opacity=1,
texRes=128, interpolate=True, depth=-1.0)

# Initialize components for Routine "trial1"
trial1Clock = core.Clock()
image_2 = visual.ImageStim(win=win, name='image_2', units='deg',
image='sin', mask=None,
ori=0, pos=[0, 0], size=[10, 10],
color=[1,1,1], colorSpace='rgb', opacity=1,
flipHoriz=False, flipVert=False,
texRes=128, interpolate=True, depth=0.0
grating_4 = visual.GratingStim(win=win, name='grating_4', units='deg',
tex='sin', mask='circle',
ori=0, pos=[0, 0], size=[0.5, 0.5], sf=0, phase=0.0,
color=[1,1,1], colorSpace='rgb', opacity=1,
texRes=128, interpolate=True, depth=-1.0)

# Initialize components for Routine "rest"
restClock = core.Clock()
grating_2 = visual.GratingStim(win=win, name='grating_2', units='deg',
tex='sin', mask='circle',
ori=0, pos=[0, 0], size=[0.5, 0.5], sf=0, phase=0.0,
color=[1,1,1], colorSpace='rgb', opacity=1,
texRes=128, interpolate=True, depth=0.0)

# Initialize components for Routine "ButtonPress"
ButtonPressClock = core.Clock()
polygon = visual.Rect(win=win, name='polygon', units='deg',
width=[10, 10][0], height=[10, 10][1],
ori=0, pos=[0, 0],
linewidth=1, lineColor=[1,1,1], lineColorSpace='rgb',
fillColor=[1,0,0], fillColorSpace='rgb',
opacity=1, interpolate=True)

# Initialize components for Routine "Thank_you"
Thank_youClock = core.Clock()
text_6 = visual.TextStim(win=win, ori=0, name='text_6',
text='End of experiment\n\nThank you!', font='Arial',
pos=[0, 0], height=0.1, wrapWidth=None,
```
Appendix 6 (continued). fMRI task script

    color='white', colorSpace='rgb', opacity=1, depth=0.0)

# Create some handy timers
global>clock = core.Clock()  # to track the time since experiment started
routineTimer = core.CountdownTimer()  # to track time remaining of each (non-slip) routine

#-------Prepare to start Routine "Instr4"-------
t = 0
Instr4Clock.reset()  # clock
frameN = -1
# update component parameters for each repeat
key_resp_4 = event.BuilderKeyResponse()  # create an object of type KeyResponse
key_resp_4.status = NOT_STARTED
# keep track of which components have finished
Instr4Components = []
Instr4Components.append(text_4)
Instr4Components.append(key_resp_4)
for thisComponent in Instr4Components:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#-------Start Routine "Instr4"-------
continueRoutine = True
while continueRoutine:
    # get current time
    t = Instr4Clock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *text_4* updates
    if t >= 0.0 and text_4.status == NOT_STARTED:
        # keep track of start time/frame for later
        text_4.tStart = t  # underestimates by a little under one frame
        text_4.frameNStart = frameN  # exact frame index
        text_4.setAutoDraw(True)

    # *key_resp_4* updates
    if t >= 0.0 and key_resp_4.status == NOT_STARTED:
        # keep track of start time/frame for later
        key_resp_4.tStart = t  # underestimates by a little under one frame
        key_resp_4.frameNStart = frameN  # exact frame index
        key_resp_4.status = STARTED
        # keyboard checking is just starting
key_res_4.clock.reset()  # now t=0
event.clearEvents(eventType='keyboard')
if key_res_4.status == 'STARTED':
    theseKeys = event.getKeys()

# check for quit:
if "escape" in theseKeys:
    endExpNow = True
if len(theseKeys) > 0:  # at least one key was pressed
    key_res_4.keys = theseKeys[-1]  # just the last key pressed
    key_res_4.rt = key_res_4.clock.get_time()
# a response ends the routine
continueRoutine = False

# check if all components have finished
if not continueRoutine:  # a component has requested a forced-end of Routine
    routineTimer.reset()  # if we abort early the non-slip timer needs reset
    break
continueRoutine = False  # will revert to True if at least one component still running
for thisComponent in Instr4Components:
    if hasattr(thisComponent, "status") and thisComponent.status != 'FINISHED':
        continueRoutine = True
        break  # at least one component has not yet finished

# check for quit (the Esc key)
if endExpNow or event.getKeys(keyList=['escape']):
    core.quit()

# refresh the screen
if continueRoutine:  # don't flip if this routine is over or we'll get a blank screen
    win.flip()
else:  # this Routine was not non-slip safe so reset non-slip timer
    routineTimer.reset()

#------Ending Routine "Instr4"------
for thisComponent in Instr4Components:
    if hasattr(thisComponent, "setAutoDraw"):
        thisComponent.setAutoDraw(False)

# check responses
if key_res_4.keys in ['', [], None]:  # No response was made
    key_res_4.keys = None

# store data for thisExp (ExperimentHandler)
Appendix 6 (continued). fMRI task script

```python
thisExp.addData('key_respons_4.keys', key_respons_4.keys)
if key_respons_4.keys != None:  # we had a response
    thisExp.addData('key_respons_4.rt', key_respons_4.rt)
thisExp.nextEntry()

# ------Prepare to start Routine "waitForTrigger"------
T = 0
waitForTriggerClock.reset()  # clock
frameN = -1
# update component parameters for each repeat
key_respons_5 = event.BuilderKeyResponse()  # create an object of type
    KeyResponse
key_respons_5.status = NOT_STARTED  # keep track of which components have finished
    waitForTriggerComponents = []
waitForTriggerComponents.append(grating)
waitForTriggerComponents.append(key_respons_5)
for thisComponent in waitForTriggerComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

# ------Start Routine "waitForTrigger"------
continueRoutine = True
while continueRoutine:
    # get current time
    t = waitForTriggerClock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *grating* updates
    if t >= 0.0 and grating.status == NOT_STARTED:
        # keep track of start time/frame for later
        grating.tStart = t  # not accounting for scr refresh
        grating.frameNStart = frameN  # exact frame index
        grating.setAutoDraw(True)

    # *key_respons_5* updates
    if t >= 0.0 and key_respons_5.status == NOT_STARTED:
        # keep track of start time/frame for later
        key_respons_5.tStart = t  # not accounting for scr refresh
        key_respons_5.frameNStart = frameN  # exact frame index
        key_respons_5.status = STARTED
        # keyboard checking is just starting
        key_respons_5.clock.reset()  # now t=0
        event.clearEvents(eventType='keyboard')
    if key_respons_5.status == STARTED:
```

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Appendix 6 (continued). fMRI task script

theseKeys = event.getKeys(keyList=['5'])

# check for quit:
if "escape" in theseKeys:
    endExpNow = True
if len(theseKeys) > 0:  # at least one key was pressed
    key_resp_5.keys = theseKeys[-1]  # just the last key pressed
    key_resp_5.rt = key_resp_5.clock.getTime()
# a response ends the routine
    continueRoutine = False

# check if all components have finished
if not continueRoutine:  # a component has requested a forced-end of Routine
    routineTimer.reset()  # if we abort early the non-slip timer needs reset
    break
    continueRoutine = False  # will revert to True if at least one component still running
    for thisComponent in waitForTriggerComponents:
        if hasattr(thisComponent, "status") and thisComponent.status != FINISHED:
            continueRoutine = True
            break  # at least one component has not yet finished

# check for quit (the Esc key)
if endExpNow or event.getKeys(keyList=['escape']):
    core.quit()

# refresh the screen
if continueRoutine:  # don't flip if this routine is over or we'll get a blank screen
    win.flip()
else:  # this Routine was not non-slip safe so reset non-slip timer
    routineTimer.reset()

#------Ending Routine "waitForTrigger"------
for thisComponent in waitForTriggerComponents:
    thisComponent.setAutoDraw(False)

# check responses
if key_resp_5.keys in [None]:  # No response was made
    key_resp_5.keys = None
# store data for thisExp (ExperimentHandler)
thisExp.addData('key_resp_5.keys', key_resp_5.keys)
if key_resp_5.keys != None:  # we had a response
    thisExp.addData('key_resp_5.rt', key_resp_5.rt)
Appendix 6 (continued). fMRI task script

thisExp.nextEntry()

# set up handler to look after randomisation of conditions etc
trials = data.TrialHandler(nReps=20, method='random',
                           extraInfo=expInfo,
                           originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.psysxp',
                           trialList=[None],
                           seed=None, name='trials')
thisExp.addLoop(trials)  # add the loop to the experiment
thisTrial = trials.trialList[0]  # so we can initialise stimuli with some values

# abbreviate parameter names if possible (e.g. rgb=thisTrial.rgb)
if thisTrial != None:
    for paramName in thisTrial.keys():
        exec(paramName + ' = thisTrial.' + paramName)

for thisTrial in trials:
    currentLoop = trials

    # abbreviate parameter names if possible (e.g. rgb = thisTrial.rgb)
    if thisTrial != None:
        for paramName in thisTrial.keys():
            exec(paramName + ' = thisTrial.' + paramName)

    # set up handler to look after randomisation of conditions etc
    condSelection = data.TrialHandler(nReps=1, method='random',
                                       extraInfo=expInfo,
                                       originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.psysxp',
                                       trialList=data.importConditions('Conditions.xlsx',
                                                                       selection=random(1)*10),
                                       seed=None, name='condSelection')
    thisExp.addLoop(condSelection)  # add the loop to the experiment

    thisCondSelection = condSelection.trialList[0]  # so we can initialise stimuli with some values

    # abbreviate parameter names if possible (e.g. rgb=thisCondSelection.rgb)
    if thisCondSelection != None:
        for paramName in thisCondSelection.keys():
            exec(paramName + ' = thisCondSelection.' + paramName)

    for thisCondSelection in condSelection:
        currentLoop = condSelection

        # abbreviate parameter names if possible (e.g. rgb =
        if thisCondSelection != None:
            for paramName in thisCondSelection.keys():
                # the contents of this block are ignored
                pass
exec(paramName + '=' + thisCondSelection.' + paramName)

#------Prepare to start Routine "selectCondition"------
t = 0
selectConditionClock.reset() # clock
frameN = -1
# update component parameters for each repeat

# keep track of which components have finished
selectConditionComponents = []
for thisComponent in selectConditionComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#------Start Routine "selectCondition"------
continueRoutine = True
while continueRoutine:
    # get current time
    t = selectConditionClock.getTime()
    frameN = frameN + 1 # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # check if all components have finished
    if not continueRoutine: # a component has requested a forced-end of Routine
        routineTimer.reset() # if we abort early the non-slip timer needs reset
        break
    continueRoutine = False # will revert to True if at least one component still running
    for thisComponent in selectConditionComponents:
        if hasattr(thisComponent, "status") and thisComponent.status != FINISHED:
            continueRoutine = True
            break # at least one component has not yet finished

    # check for quit (the Esc key)
    if endExpNow or event.getKeys(keyList=['escape']):
        core.quit()

    # refresh the screen
    if continueRoutine: # don't flip if this routine is over or we'll get a blank screen
        win.flip()
    else: # this Routine was not non-slip safe so reset non-slip timer
Appendix 6 (continued). fMRI task script

routineTimer.reset()

#------- Ending Routine "selectCondition"-------
for thisComponent in selectConditionComponents:
    if hasattr(thisComponent, "setAutoDraw"):
        thisComponent.setAutoDraw(False)
if condSelect=='S':
    nRepsSem=np.random.randint(3,10)
    nRepsAut=0
    nRepsButtonPress=0
    nRepsFix=0

elif condSelect=='A':
    nRepsSem=0
    nRepsAut=np.random.randint(3,10)
    nRepsButtonPress=0
    nRepsFix=0

elif condSelect=='X':
    nRepsSem=0
    nRepsButtonPress=1
    nRepsAut=0
    nRepsFix=0

else:
    nRepsSem=0
    nRepsAut=0
    nRepsFix=np.random.randint(3,10)
    nRepsButtonPress=0

thisExp.nextEntry()

# completed 1 repeats of 'condSelection'

# set up handler to look after randomisation of conditions etc
RepsSem = data.TrialHandler(nReps=nRepsSem, method='random',
extraInfo=expInfo,
originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.pyse
xp',
trialList=data.importConditions('trialTypesMaster.xlsx',
selection=random(1)*40),
seed=None, name='RepsSem')
thisExp.addLoop(RepsSem)  # add the loop to the experiment
thisRepsSem = RepsSem.trialList[0]  # so we can initialise stimuli with some values
Appendix 6 (continued). fMRI task script

```plaintext
# abbreviate parameter names if possible (e.g. rgb=thisRepsSem.rgb)
if thisRepsSem != None:
    for paramName in thisRepsSem.keys():
        exec(paramName + ' = thisRepsSem.' + paramName)

for thisRepsSem in RepsSem:
    currentLoop = RepsSem
    # abbreviate parameter names if possible (e.g. rgb = thisRepsSem.rgb)
    if thisRepsSem != None:
        for paramName in thisRepsSem.keys():
            exec(paramName + ' = thisRepsSem.' + paramName)

    # set up handler to look after randomisation of conditions etc
    selectImageSem = data.TrialHandler(nReps=1, method='random',
                                       extraInfo=expInfo,
                                       originPath='C:\Users\user\Desktop\PFT_fMRI\LanguageTask234.psyexp',
                                       trialList=data.importConditions('trialTypesMaster.xlsx',
                                                                 selection=random(1)*40),
                                       seed=None, name='selectImageSem')
    thisExp.addLoop(selectImageSem)  # add the loop to the experiment
    thisSelectImageSem = selectImageSem.trialList[0]  # so we can initialise stimuli with some values
    # abbreviate parameter names if possible (e.g.
    rgb=thisSelectImageSem.rgb)
    if thisSelectImageSem != None:
        for paramName in thisSelectImageSem.keys():
            exec(paramName + ' = thisSelectImageSem.' + paramName)

    for thisSelectImageSem in selectImageSem:
        currentLoop = selectImageSem
        # abbreviate parameter names if possible (e.g. rgb = thisSelectImageSem.rgb)
        if thisSelectImageSem != None:
            for paramName in thisSelectImageSem.keys():
                exec(paramName + ' = thisSelectImageSem.' + paramName)

        #------Prepare to start Routine "trial"------
        t = 0
        trialClock.reset()  # clock
        frameN = -1
        routineTimer.add(3.000000)
        # update component parameters for each repeat
        Stim.setImage(image)
```

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Appendix 6 (continued). fMRI task script

```python
# keep track of which components have finished
trialComponents = []
trialComponents.append(Stim)
trialComponents.append(grating_3)
for thisComponent in trialComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#-------Start Routine "trial"-------
continueRoutine = True
while continueRoutine and routineTimer.getTime() > 0:
    # get current time
    t = trialClock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *Stim* updates
    if t >= 0.0 and Stim.status == NOT_STARTED:
        # keep track of start time/frame for later
        Stim.tStart = t  # underestimates by a little under one frame
        Stim.frameNStart = frameN  # exact frame index
        Stim.setAutoDraw(True)
    if Stim.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  #most of one frame period left
        Stim.setAutoDraw(False)

    # *grating_3* updates
    if t >= 0.0 and grating_3.status == NOT_STARTED:
        # keep track of start time/frame for later
        grating_3.tStart = t  # underestimates by a little under one frame
        grating_3.frameNStart = frameN  # exact frame index
        grating_3.setAutoDraw(True)
    if grating_3.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  #most of one frame period left
        grating_3.setAutoDraw(False)

    # check if all components have finished
    if not continueRoutine: # a component has requested a forced-end of Routine
        routineTimer.reset() # if we abort early the non-slipp timer
        break
    continueRoutine = False # will revert to True if at least one component still running
```

444
for thisComponent in trialComponents:
    if hasattr(thisComponent, "status") and
    thisComponent.status != FINISHED:
        continueRoutine = True
        break  # at least one component has not yet finished

# check for quit (the Esc key)
if endExpNow or event.getKeys(keyList=['escape']):
    core.quit()

# refresh the screen
if continueRoutine:  # don't flip if this routine is over or we'll get a blank screen
    win.flip()

        #------Ending Routine "trial"------
        for thisComponent in trialComponents:
            if hasattr(thisComponent, "setAutoDraw"):
                thisComponent.setAutoDraw(False)
        thisExp.nextEntry()

# completed 1 repeats of 'selectImageSem'
thisExp.nextEntry()

# completed nRepsSem repeats of 'RepsSem'

# set up handler to look after randomisation of conditions etc
RepsAut = data.TrialHandler(nReps=nReps, method='random',
    extraInfo=expInfo, originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.psyexp',
    trialList=data.importConditions('trialTypesMasterS.xlsx',
    selection=random(1)*40),
    seed=None, name='RepsAut')
thisExp.addLoop(RepsAut)  # add the loop to the experiment
thisRepsAut = RepsAut.trialList[0]  # so we can initialise stimuli with some values
# abbreviate parameter names if possible (e.g. rgb=thisRepsAut.rgb)
if thisRepsAut != None:
    for paramName in thisRepsAut.keys():
        exec(paramName + '=' + str(thisRepsAut[paramName]))

for thisRepsAut in RepsAut:
    currentLoop = RepsAut
Appendix 6 (continued). fMRI task script

```python
# abbreviate parameter names if possible (e.g. rgb = thisRepsAut.rgb)
if thisRepsAut != None:
    for paramName in thisRepsAut.keys():
        exec(paramName + '=' + thisRepsAut.' + paramName)

# set up handler to look after randomisation of conditions etc
selectImageAut = data.TrialHandler(nReps=1, method='random',
extraInfo=expInfo,
originPath='C:\\Users\user\\Desktop\\PFT_fMRI\\LanguageTask234.psyexp',
trialList=data.importConditions('trialTypesMasterS.xlsx',
selection=random(1)*40),
seed=None, name='selectImageAut')
thisExp.addLoop(selectImageAut) # add the loop to the experiment
thisSelectImageAut = selectImageAut.trialList[0] # so we can initialise stimuli with some values
# abbreviate parameter names if possible (e.g.
rgb=thisSelectImageAut.rgb)
if thisSelectImageAut != None:
    for paramName in thisSelectImageAut.keys():
        exec(paramName + '=' + thisSelectImageAut.' + paramName)

for thisSelectImageAut in selectImageAut:
    currentLoop = selectImageAut
    # abbreviate parameter names if possible (e.g. rgb =
thisSelectImageAut.rgb)
    if thisSelectImageAut != None:
        for paramName in thisSelectImageAut.keys():
            exec(paramName + '=' + thisSelectImageAut.' + paramName)

    #------Prepare to start Routine "trial1"------
    t = 0
    trial1Clock.reset() # clock
    frameN = -1
    routineTimer.add(3.000000)
    # update component parameters for each repeat
    image_2.setImage(image)
    # keep track of which components have finished
    trial1Components = []
    trial1Components.append(image_2)
    trial1Components.append(grating_4)
    for thisComponent in trial1Components:
        if hasattr(thisComponent, 'status'):
            thisComponent.status = NOT_STARTED

    #------Start Routine "trial1"------
```

continueRoutine = True
while continueRoutine and routineTimer.getTime() > 0:
    # get current time
    t = trial1Clock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame
    # *image_2* updates
    if t >= 0.0 and image_2.status == NOT_STARTED:
        # keep track of start time/frame for later
        image_2.tStart = t  # underestimates by a little under one frame
        image_2.frameNStart = frameN  # exact frame index
        image_2.setAutoDraw(True)
    if image_2.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  # most of one frame period left
        image_2.setAutoDraw(False)
    # *grating_4* updates
    if t >= 0.0 and grating_4.status == NOT_STARTED:
        # keep track of start time/frame for later
        grating_4.tStart = t  # underestimates by a little under one frame
        grating_4.frameNStart = frameN  # exact frame index
        grating_4.setAutoDraw(True)
    if grating_4.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  # most of one frame period left
        grating_4.setAutoDraw(False)
    # check if all components have finished
    if not continueRoutine:  # a component has requested a forced-end of Routine
        break
    continueRoutine = False  # will revert to True if at least one component still running
    for thisComponent in trial1Components:
        if hasattr(thisComponent, "status") and thisComponent.status != FINISHED:
            continueRoutine = True
            break  # at least one component has not yet finished

    # check for quit (the Esc key)
    if endExpNow or event.getKeys(keyList=['escape']):
        core.quit()
Appendix 6 (continued). fMRI task script

# refresh the screen
if continueRoutine:  # don't flip if this routine is over or we'll get a blank screen
    win.flip()

#-------Ending Routine "trial1"-------
for thisComponent in trial1Components:
    if hasattr(thisComponent, "setAutoDraw"): thisComponent.setAutoDraw(False)
thisExp.nextEntry()

# completed 1 repeats of 'selectImageAut'
thisExp.nextEntry()

# completed nRepsAut repeats of 'RepsAut'

# set up handler to look after randomisation of conditions etc
RepsFix = data.TrialHandler(nReps=nRepsFix, method='random', extraInfo=expInfo, originPath='C:\\Users\\user\\Desktop\\PFT_fMRI\\LanguageTask234.psyexp',
    trialList=[None],
    seed=None, name='RepsFix')
thisExp.addLoop(RepsFix) # add the loop to the experiment
thisRepsFix = RepsFix.trialList[0] # so we can initialise stimuli with some values
# abbreviate parameter names if possible (e.g. rgb=thisRepsFix.rgb)
if thisRepsFix != None:
    for paramName in thisRepsFix.keys():
        exec(paramName + '=' + thisRepsFix[paramName])

for thisRepsFix in RepsFix:
    currentLoop = RepsFix
    # abbreviate parameter names if possible (e.g. rgb =
    thisRepsFix.rgb)
    if thisRepsFix != None:
        for paramName in thisRepsFix.keys():
            exec(paramName + '=' + thisRepsFix[paramName])

    #-------Prepare to start Routine "rest"-------
t = 0
restClock.reset() # clock
frameN = -1
routineTimer.add(3.000000)
Appendix 6 (continued). fMRI task script

```python
# update component parameters for each repeat
# keep track of which components have finished
restComponents = []
restComponents.append(grating_2)
for thisComponent in restComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#-------Start Routine "rest"-------
continueRoutine = True
while continueRoutine and routineTimer.getTime() > 0:
    # get current time
    t = restClock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *grating_2* updates
    if t >= 0.0 and grating_2.status == NOT_STARTED:
        # keep track of start time/frame for later
        grating_2.tStart = t  # underestimates by a little under one frame
        grating_2.frameNStart = frameN  # exact frame index
        grating_2.setAutoDraw(True)
    if grating_2.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  # most of one frame period left
        grating_2.setAutoDraw(False)

    # check if all components have finished
    if not continueRoutine:  # a component has requested a forced-end of Routine
        routineTimer.reset()  # if we abort early the non-slip timer
        break
    continueRoutine = False  # will revert to True if at least one component still running
    for thisComponent in restComponents:
        if hasattr(thisComponent, "status") and thisComponent.status != FINISHED:
            continueRoutine = True
            break  # at least one component has not yet finished

    # check for quit (the Esc key)
    if endExpNow or event.getKeys(keyList=['escape']):
        core.quit()

    # refresh the screen
```
Appendix 6 (continued). fMRI task script

```python
if continueRoutine:  # don't flip if this routine is over or we'll get
    win.flip()

#-------Ending Routine "rest"-------
for thisComponent in restComponents:
    if hasattr(thisComponent, "setAutoDraw"):  
        thisComponent.setAutoDraw(False)
thisExp.nextEntry()

# completed nRepsFix repeats of 'RepsFix'

# set up handler to look after randomisation of conditions etc
RepsButtonPress = data.TrialHandler(nReps=nRepsButtonPress, method='random',
    extraInfo=expInfo, originPath='C:\Users\user\Desktop\PFT_fMRI\LanguageTask234.psyexp',
    trialList=[None],
    seed=None, name='RepsButtonPress')
thisExp.addLoop(RepsButtonPress)  # add the loop to the experiment
thisRepsButtonPress = RepsButtonPress.trialList[0]  # so we can
initialise stimuli with some values
# abbreviate parameter names if possible (e.g.
rgb=thisRepsButtonPress.rgb
if thisRepsButtonPress != None:
    for paramName in thisRepsButtonPress.keys():
        exec(paramName + ' = thisRepsButtonPress.' + paramName)

for thisRepsButtonPress in RepsButtonPress:
    currentLoop = RepsButtonPress
    # abbreviate parameter names if possible (e.g. rgb =
thisRepsButtonPress.rgb
    if thisRepsButtonPress != None:
        for paramName in thisRepsButtonPress.keys():
            exec(paramName + ' = thisRepsButtonPress.' + paramName)

#-------Prepare to start Routine "ButtonPress"-------
t = 0
ButtonPressClock.reset()  # clock
frameN = -1
routineTimer.add(3.000000)
# update component parameters for each repeat
# keep track of which components have finished
ButtonPressComponents = []
ButtonPressComponents.append(polygon)
```
Appendix 6 (continued). fMRI task script

for thisComponent in ButtonPressComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#-------Start Routine "ButtonPress"-------
continueRoutine = True
while continueRoutine and routineTimer.getTime() > 0:
    # get current time
    t = ButtonPressClock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *polygon* updates
    if t >= 0.0 and polygon.status == NOT_STARTED:
        # keep track of start time/frame for later
        polygon.tStart = t  # underestimates by a little under one frame
        polygon.frameNStart = frameN  # exact frame index
        polygon.setAutoDraw(True)
    if polygon.status == STARTED and t >= (0.0 + (3.0-win.monitorFramePeriod*0.75)):  #most of one frame period left
        polygon.setAutoDraw(False)

    # check if all components have finished
    if not continueRoutine:  # a component has requested a forced-end of Routine
        routineTimer.reset()  # if we abort early the non-slip timer needs reset
        break
    continueRoutine = False  # will revert to True if at least one component still running
    for thisComponent in ButtonPressComponents:
        if hasattr(thisComponent, "status") and thisComponent.status != FINISHED:
            continueRoutine = True
            break  # at least one component has not yet finished

    # check for quit (the Esc key)
    if endExpNow or event.getKeys(keyList=['escape']):
        core.quit()

    # refresh the screen
    if continueRoutine:  # don't flip if this routine is over or we'll get a blank screen
        win.flip()
Appendix 6 (continued). fMRI task script

# --------Ending Routine "ButtonPress"--------
for thisComponent in ButtonPressComponents:
    if hasattr(thisComponent, "setAutoDraw"):
        thisComponent.setAutoDraw(False)
thisExp.nextEntry()

# completed nRepsButtonPress repeats of 'RepsButtonPress'
thisExp.nextEntry()

# completed 20 repeats of 'trials'

#--------Prepare to start Routine "Thank_you"--------
t = 0
Thank_youClock.reset() # clock
frameN = -1
# update component parameters for each repeat
# keep track of which components have finished
Thank_youComponents = []
Thank_youComponents.append(text_6)
for thisComponent in Thank_youComponents:
    if hasattr(thisComponent, 'status'):
        thisComponent.status = NOT_STARTED

#--------Start Routine "Thank_you"--------
continueRoutine = True
while continueRoutine:
    # get current time
    t = Thank_youClock.getTime()
    frameN = frameN + 1  # number of completed frames (so 0 is the first frame)
    # update/draw components on each frame

    # *text_6* updates
    if t >= 0.0 and text_6.status == NOT_STARTED:
        # keep track of start time/frame for later
text_6.tStart = t # underestimates by a little under one frame
text_6.frameNStart = frameN # exact frame index
text_6.setAutoDraw(True)

    # check if all components have finished
    if not continueRoutine:  # a component has requested a forced-end of Routine
        routineTimer.reset() # if we abort early the non-slipping timer needs reset
        break

    # refresh the screen
    thisExp.flip()
Appendix 6 (continued). fMRI task script

    continueRoutine = False  # will revert to True if at least one
    for thisComponent in Thank_youComponents:
        if hasattr(thisComponent, "status") and thisComponent.status !=
    FINISHED:
        continueRoutine = True
        break  # at least one component has not yet finished

    # check for quit (the Esc key)
    if endExpNow or event.getKeys(keyList=['escape']):
        core.quit()

    # refresh the screen
    if continueRoutine:  # don't flip if this routine is over or we'll get a
        win.flip()
    else:  # this Routine was not non-slip safe so reset non-slip timer
        routineTimer.reset()

    #------Ending Routine "Thank_you"------
    for thisComponent in Thank_youComponents:
        if hasattr(thisComponent, "setAutoDraw"):
            thisComponent.setAutoDraw(False)

    win.close()
    core.quit()
Appendix 7. Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 7 (continued). Images used in fMRI task
Appendix 8. fMRI task instructions

Instruction screen one

Hello!

In this experiment you will be asked to say words SILENTLY in your mind. Please do not move your mouth or head.

KEEP AS STILL AS YOU CAN!

Press any button to continue

Instruction screen two

Try to keep your eyes on the white dot all the time.

Follow the instructions you received before the scan

Remember: KEEP AS STILL AS YOU CAN!

Press any button to continue

Instruction screen three

Are you ready?

Press any button to start the experiment
Appendix 9. fMRI first level analysis example timing file and design matrix

| 36.1665 | 24.0415 | 1  |
| 129.3791| 24.042  | 1  |
| 171.5032| 12.0391 | 1  |
| 237.6601| 12.0391 | 1  |

Example of a timing file. First column represents the condition onset time in relation to the start of the task in seconds; second column - duration of the epoch in seconds, third column – value of the input during the specified period.

Example of a design matrix used in the first-level fMRI analysis. 106 first level analyses were performed in total (typically three per subject, in two cases two per subject)

<table>
<thead>
<tr>
<th></th>
<th>C1 Semantic Retrieval</th>
<th>C2 Covert Articulation</th>
<th>C3 Button Press</th>
<th>C4 Hear Language</th>
<th>C5 Sen&gt;Art</th>
<th>C6 Art&gt;Sem</th>
</tr>
</thead>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 10. fMRI second level analysis design matrix. One contrast per participant.
Appendix 11. fMRI third level analysis design matrix.

Group A – healthy controls, group B - patients

<table>
<thead>
<tr>
<th></th>
<th>group A &gt; group B</th>
<th>group B &gt; group A</th>
<th>group A mean</th>
<th>group B mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>-1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C3</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 12. Whole-brain voxel-wise regression analyses of the predictive value of LCI on the change in signal during Semantic Retrieval condition: design matrix. Contrast 3 is of particular interest as it displays clusters where higher LCI is associated with higher signal intensity.

<table>
<thead>
<tr>
<th></th>
<th>HV &gt; Ps LCI-adjusted</th>
<th>Ps &gt; HV LCI adjusted</th>
<th>Pos LCI effect</th>
<th>Neg LCI effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
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<td>-1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 13. Interaction analysis design matrix to assess whether the association between LCI and signal change during Semantic Retrieval is different for patients and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>HV</th>
<th>Ps</th>
<th>LCI_HV</th>
<th>LCI_Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>SlopeHV &gt; Ps LCI</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C2</td>
<td>SlopePs &gt; HV LCI</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>
Appendix 14. Whole-brain voxel-wise regression analyses of the predictive value of ELI on the change in signal during Covert Articulation condition: design matrix. Contrast 3 is of particular interest as it displays clusters where higher ELI is associated with higher signal intensity.
Appendix 15. Interaction analysis design matrix to assess whether the association between ELI and signal change during Covert Articulation is different for patients and healthy controls

<table>
<thead>
<tr>
<th>C1</th>
<th>SlopeHV &gt; Ps ELI</th>
<th>HV</th>
<th>Ps</th>
<th>ELI_HV</th>
<th>ELI_Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>Slope Ps &gt; HV ELI</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix 16. Whole-brain voxel-wise regression analyses of the predictive value of LCI on the change in signal during Semantic Retrieval condition, adjusted for non-verbal IQ: design matrix

<table>
<thead>
<tr>
<th></th>
<th>HV</th>
<th>Ps</th>
<th>LCI</th>
<th>RPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>HV &gt; Ps LCI-adjusted</td>
<td>1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>Ps &gt; HV LCI adjusted</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C3</td>
<td>Pos LCI effect adjusted for RPM</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>Neg LCI effect adjusted for RPM</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>
Appendix 17. Whole-brain voxel-wise regression analyses of the predictive value of ELI on the change in signal during Covert Articulation condition, adjusted for non-verbal IQ: design matrix

<table>
<thead>
<tr>
<th></th>
<th>MV</th>
<th>Fs</th>
<th>ELI</th>
<th>RPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>MV &gt; Fs ELI controlled</td>
<td>1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>Fs &gt; MV ELI controlled</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C3</td>
<td>ELI pos effect adjusted for RPM</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>ELI neg effect adjusted for RPM</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>
Appendix 18. Analysis of the cerebellar activation in healthy controls. Design matrix was the same for the Semantic Retrieval and Covert Articulation analyses.
Appendix 19. Analyses of the between-group differences in DTI measures. Design matrix is the same for all scalars (FA, MD, RA and AD) and all ROIs (Whole brain, SCP and AF). Group A – healthy controls, group B – patients

<table>
<thead>
<tr>
<th></th>
<th>group A &gt; group B</th>
<th></th>
<th>group B &gt; group A</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>1</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>-1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 20. Regression analyses of the predictive values of the WM microstructure on Language Content Index in a patient group. Design matrix is the same for FA, MD, RD and AD

<table>
<thead>
<tr>
<th>Mean</th>
<th>PS</th>
<th>LCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>LCI_positive</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 21. Regression analyses of the predictive values of the WM microstructure on Expressive Language Index in a patient group. Design matrix is the same for FA, MD, RD and AD.

<table>
<thead>
<tr>
<th>C1</th>
<th>Mean</th>
<th>PS</th>
<th>ELI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELI_positive</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>