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A Neuropsychological Assessment of Children Treated with Prophylactic Cranial Irradiation for Acute Leukaemia

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A dissertation submitted in complete fulfillment of the requirements for the degree of Master of Arts in Psychology by Dissertation

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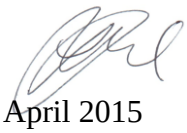
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Chapter 1: Introduction

1.1 Research Aims

The purpose of this study was to expand on the scope and findings of the original study conducted by Whitaker and Schutte (2012), which investigated memory and learning in children with a history of acute lymphoblastic leukaemia (ALL). The present study aimed to investigate the full complement of neuropsychological functions, namely social-emotional functioning, intelligence, executive functioning, and memory, in a larger sample of children with a history acute leukaemia. In order to obtain a larger sample than in the previous study, the researcher included a second type of acute leukaemia in the present study, namely acute myeloblastic leukaemia (AML). By increasing the sample size and expanding the psychological test battery, the present study aimed to investigate the issue of cognitive impairment within a broader context in the paediatric leukaemia population. The wider scope of this study allowed the traits previously investigated to be contextualised within a broader spectrum of neuropsychological functions, and also in accordance with radiation dosage.

1.2 Rationale

Acute leukaemia is the most common type of cancer in South African children, accounting for 25,4% of all cancer diagnoses in the paediatric population (Hesseling et al., 2004; Stefan & Stones, 2012). The term “paediatric population” is used in this study to refer to children under the age of 15, who represent approximately 30% of

the total South African population (Statistics South Africa, 2012; Stefan & Stones, 2012). With improvements in the diagnosis and treatment of paediatric leukaemia in South Africa over the past 30 years, survivorship is continually increasing, and the need for local research to understand how leukaemia treatment affects brain functioning is greater than ever before (Anderson, Kunin-Batson, Perkins & Baker, 2008; Botha and Kruger, 2012).

Presently, more than 80% of South African children survive for 5 years or longer after diagnosis with acute leukaemia, and more than 70% of these survivors will continue to be long-term survivors (Botha & Kruger, 2012). This is a dramatic improvement on the survival rate of 48% between 1990 and 1999 (Poyiadjis, Wainwright, Naidu, Mackinnon & Poole, 2011). In addition to medical advancement, the reason why a larger proportion of children are surviving acute leukaemia in South Africa is partly due to increased efforts at educational awareness campaigns, which have aided in the early detection of childhood leukaemia (CHOC Childhood Cancer Foundation South Africa [CHOC], 2014a). Early detection is a key factor in the treatment of acute leukaemia, as the sooner treatment is initiated, the less of a chance the leukaemia has at invading other organs in the body and spreading out of control. The best way to detect leukaemia at an early stage is to be aware of the symptoms of the disease, which are described in the next chapter. Once the symptoms have been detected, treatment in a specialist paediatric oncology unit is essential in order to receive the necessary expertise and adequate technical equipment required for a successful outcome (European Network for Cancer Research in Children and Adolescents [ENCCA], 2013). These specialist units offer a multidisciplinary treatment approach, which includes chemotherapy, irradiation, surgery, as well as other supportive and

palliative care (Cantrell & Ruble, 2011). This multidisciplinary approach has contributed to the improved survival rates and quality of life in children with leukaemia (Cantrell & Ruble, 2011). Generally, the luxury of multidisciplinary treatment is only available in well developed countries (Cantrell & Ruble, 2011); however, South Africa is in a unique position as it has some well regarded paediatric oncology units attached to its academic teaching hospitals, where multidisciplinary treatment is practiced (CHOC, 2014b). What makes these units so effective is that they follow well-established international treatment protocols, and are run in accordance with the standards established by the International Society of Paediatric Oncology (CHOC, 2014b). As such, paediatric oncology units in South Africa are adequately equipped with resources and produce results that are comparable to international standards (CHOC, 2014b).

The increasing survivorship rate in South Africa has been accompanied by a number of survivorship issues relating to the long-term toxicity of treatment (Munch, 2013). One of the foremost issues reported by child survivors of acute leukaemia is a mild to moderate decline in cognitive function, particularly in the context of cranial irradiation (Monje, 2008). What is especially interesting about this cognitive decline is that it has a progressive and cumulative course: It is only evident 6 or more months after cranial irradiation, and tends to develop with increasing time since treatment (Daams et al., 2012; Giordano, Welzel, Abo-Madyan & Wenz, 2012; Hesselink, n.d.). The major mechanism of this cumulative progression is believed to involve structural white matter changes, and a discussion about these changes is provided in the next chapter of this paper. Given the delayed onset of cognitive impairment, researchers aptly refer to it as a “late effect” of cancer treatment. This was an important

consideration in this study. In order to control for the late onset of cognitive impairment, the researcher developed the inclusion criterion that eligible children had to have received cranial irradiation at least 6 months prior to the date of the neuropsychological assessment.

While cranial irradiation has proven to be highly effective in treating paediatric leukaemia, higher doses tend to increase the risk for late cognitive effects (Copeland, 1992). This has been a central dilemma in the paediatric leukaemia field, and a number of clinical trials have focused on designing treatment protocols that adequately treat the disease while limiting the impact on cognitive function (Cantrell & Ruble, 2011). Ongoing efforts at treatment reduction have required a delicate balance between disease-free survival and quality of life, which is becoming increasingly important in light of modern day medical advances (Anderson et al., 2008). A salient aim of this study was therefore to establish the dose of cranial irradiation at which cognitive effects are more pronounced. While there seems to be a trend of treating ALL with 18 grays (Gy) and AML with 12 Gy of cranial irradiation, this is not exclusively so, as individual risk factors also contribute to the treatment planning process. At the time in the treatment protocol when a child is due to receive cranial irradiation, a number of prognostic factors are considered in addition to diagnosis, such as age and stage of disease, which help determine the total dose of radiation a child will receive. As will be seen later in chapter 4, the 12 and 18 Gy subsamples each contained a mix of ALL and AML diagnoses. This was advantageous to this study because it somewhat eliminated the effect of differing disease processes on neuropsychological test performance. It allowed the researcher

to focus on differences pertinent to radiation dosage without significant interference from the type of acute leukaemia, which was not under investigation.

It is hoped that this study will be valuable at many levels: Firstly, it is hoped that the results of this study will motivate doctors to irradiate with reduced doses if at all possible in order to minimise the risk of long-term cognitive effects. Secondly, it is hoped that the study findings will contribute knowledge to ongoing clinical trials in which treatments for acute leukaemia are continually being refined. Thirdly, it is hoped that the study findings will facilitate early detection of late cognitive effects in child survivors, and allow for timely interventions. The suggestions made at the end of this study should ideally inform educational interventions for child survivors, as their cognitive strengths and weaknesses following treatment will be better understood (Anderson et al., 2008).

Chapter 2: Literature Review

PART I: Acute Leukaemia, the Disease and its Treatments

2.1 Overview of Acute Leukaemia

Leukaemia literally means “white blood”, and acute leukaemia refers to a rapidly advancing cancer of the white blood cells (Marieb & Hoehn, 2014). It originates in the bone marrow, which is the production site of all the blood cells in the body, namely red blood, cells, white blood cells, and platelets (Marieb & Hoehn, 2014). Once the bone marrow becomes cancerous, it produces excessive amounts of

abnormal, immature white blood cells called blasts, which flood into the bloodstream and circulate throughout the body (Marieb & Hoehn, 2014). A typical white blood cell functions in the immune response and is specialised to defend the body against infection (Marieb & Hoehn, 2014). However, blasts do not mature correctly, remaining unspecialised and nonfunctional (Marieb & Hoehn, 2014). As such, recurrent infection is a hallmark symptom of acute leukaemia (Goldsmith, 2012). Blasts also divide rapidly and proliferate out of control, crowding out other blood cell lines in the body (Marieb & Hoehn, 2014). It is for this reason that children with acute leukaemia tend to have symptoms of anaemia (shortage of red blood cells) and easy bleeding (shortage of platelets) (Goldsmith, 2012).

The leukaemias are named according to the type of white blood cell primarily affected (Marieb & Hoehn, 2014). When the lymphoid white blood cells are affected, the leukaemia is named ALL, and when the myeloid white blood cells are affected, the leukaemia is named AML (Marieb & Hoehn, 2014). What distinguishes ALL and AML from solid tumors is that they are blood-borne cancers and, unlike solid tumors, leukaemias are not localised. Since the blood circulates past every organ in the body, the blasts only need to break through the capillary wall and invade the surrounding tissues in order to form another cancer. From a disease management perspective, early diagnosis and treatment are critical in preventing the spread of the leukaemia in this way.

Although ALL and AML are the two major types of acute leukaemia, it is important to acknowledge the subtypes that exist for both types of acute leukaemia. The subtypes have been described below purely for background purposes, as they were not

of practical importance to this study. The reason for this is that the subtypes are treated in more or less the same way (B. Goodwin, personal communication, March 5, 2014). This was advantageous to the present study, as the sample size of 20 did not allow for analyses to be conducted based on subtype.

Acute lymphoblastic leukaemia can either arise in immature B lymphocytes, which are antibody-producing cells, or immature T lymphocytes, which are cytotoxic cells (Marieb & Hoehn, 2014). Depending on the type of lymphocyte affected, ALL is classified as B cell or T cell ALL. Pre-B cell ALL, which is the most common form of B cell ALL, accounts for 80% of paediatric ALL cases. By contrast, T cell ALL is a more rare subtype and accounts for only 15% of paediatric ALL cases (Albitar, Giles & Kantarjian, 2008). In terms of the major differences between the two subtypes of ALL, T cell ALL is associated with a lower rate of remission (symptom-free period), as it tends to be more resistant to treatment (Chiaretti & Foa, 2009; Goldberg et al., 2003). The drug resistance of T cell ALL is seen in the higher rates of early treatment failure and early relapse (reappearance of leukaemic blasts), which occurs most commonly in the bone marrow but also frequently in the central nervous system (CNS) (Goldberg et al., 2003). The mechanism of resistance may be attributed to a higher white blood cell count at diagnosis, making T cell ALL harder to treat effectively (Goldberg et al., 2003).

Acute myeloblastic leukaemia occurs in the blood-forming cells that are destined to become white blood cells other than lymphocytes (American Cancer Society, 2013). Most subtypes of AML arise in immature white blood cells but on rare occasions, AML may arise in immature red blood cells or platelets (American Cancer Society,

2013). The subtypes of AML are traditionally named according to the French American British classification system, which lists 8 subtypes of AML, ranging from M0 to M7 (American Cancer Society, 2013). Morphology is the key criterion by which AML classification is made, which takes into consideration the maturity of the leukaemic blasts as well as the type of blood cell affected (Meshinchi & Arceci, 2007). Subtypes M0 through M5 arise in immature white blood cells, with M2 being the most common subtype of paediatric AML (American Cancer Society, 2014). Subtypes M6 and M7 arise in immature red blood cells and platelets respectively (American Cancer Society, 2013). Meshinchi and Arceci (2007) list M6 AML and M7 AML as the two subtypes that are associated with the worst outcome, suggesting that AML in the red blood cells and platelets is harder to treat than AML in the white blood cells. Like T cell ALL, AML is intrinsically resistant to antileukaemic drugs (Meshinchi & Arceci, 2007). The mechanism of resistance in AML has been attributed to the expression of certain genes and proteins that mediate drug resistance (Meshinchi & Arceci, 2007). The first round of treatment is usually extremely aggressive for children with AML, in an attempt to overcome this resistance (Meshinchi & Arceci, 2007). However, the high rates of early treatment failure and early relapse commonly observed in children with T cell ALL are also observed in children with AML (Meshinchi & Arceci, 2007).

The aetiology of paediatric leukaemia is largely unknown; however, a number of studies have attempted to identify factors that predispose children to the development of acute leukaemia (Belson, Kingsley & Holmes, 2007). Genetic composition of the embryo is one such predisposing factor, where acute leukaemia may actually develop *in utero* (Belson et al., 2007). DNA mutations during the course of embryonic

development may cause bone marrow stem cells to develop into leukaemic blasts (Stefan & Stones, 2012). An interesting finding that supports a genetic cause for leukaemia is that children with inherited diseases such as Down syndrome are at increased risk for developing acute leukaemia (Goldsmith, 2012). This suggests that chromosomal abnormalities play a role in the development of leukaemia. Siblings of children with leukaemia are at higher risk than children whose siblings do not have the disease, and an identical twin is twice more likely to develop leukaemia if his or her twin developed leukaemia before the age of 7 (Belson et al., 2007). Although all of these examples point to an underlying genetic cause, most cases of leukaemia occur in healthy children, with no recognisable genetic abnormalities (American Cancer Society, 2013). In considering environmental risk factors, Belson and colleagues (2007) conducted a review and concluded that exposure to high levels of ionising radiation is the only factor in the environment that may place children at risk for acute leukaemia, particularly AML. However, this finding is largely irrelevant in the South African context, where frequent exposure to ionising radiation is rare. Exposure to certain chemicals such as benzene and household pesticides has been linked to cancer in adults; however, there is no association between benzene and childhood cancer (Belson et al., 2007). Some studies have suggested that acute leukaemia may be caused by a combination of genetic susceptibility and environmental exposure (Belson et al., 2007). For example, genetic polymorphisms may interfere with the child's ability to properly metabolise and transport certain harmful chemical substances in the body (Belson et al., 2007). Finally, some studies have investigated the relationship between immunological risk factors and the development of acute leukaemia. It has been found that children with compromised immune systems are generally more vulnerable to certain pathogens that may trigger

the development of acute leukaemia (Belson et al., 2007). This is particularly relevant in the South African context, where disease is rife in areas with high levels of poverty. The immunological risk factors may also explain why approximately 80% of paediatric cancers occur in developing countries, where population numbers are high, encouraging the rapid spread of infectious diseases (Stefan & Stones, 2012). Immunologically weak individuals are susceptible to these infectious agents, which may trigger a wave of new acute leukaemia cases in rural communities (Belson et al., 2007). A clear cause for childhood leukaemia is, however, yet to be defined. For the time being, the predisposing factors discussed above are helpful in understanding the development of the disease.

2.2 The International Acute Leukaemia Situation

In order to gain perspective on the leukaemia situation in South Africa, Albrecht (2006) suggests that it is necessary to consider the international situation as a starting point.

Internationally, acute leukaemia is the most common type of cancer in children, accounting for 30% of paediatric cancer diagnoses (Belson et al., 2007). The annual paediatric cancer incidence rate has been reported at 14 children per 100 000, which includes both leukaemias and solid tumors (Weiner, 2002). In looking at the incidence distribution, 3 to 4 cases are ALL (Belson et al., 2007) and less than one case is AML (Gilliland & Tallman, 2003). This indicates that ALL is the most common type of acute leukaemia in children, with a diagnosis rate approximately four times that of AML in the international setting. In considering treatment outcomes in developed

countries, the overall cure rate has been reported as approximately 80% for ALL and 60 to 70% for AML (ENCCA, 2013). This given, children with ALL seem to have a better success rate than children with AML, which is likely related to the intrinsic drug resistance of AML.

In terms of demographic risk factors in the international setting, age, gender, and race/ethnicity seem to play important roles in treatment outcome. The peak age of incidence for ALL is 2 to 5 years, and the peak age of incidence for AML is 1 to 4 years (Belson et al., 2007). The reason why acute leukaemia tends to be more common in the early years of life may be related to the immunological risk factors previously described. Young children have immature immune systems, which contributes to their susceptibility to childhood diseases (Belson et al., 2007). In terms of gender and ALL, male children have a lower survival rate than female children because males have a higher incidence of T cell ALL (Pui et al., 1999). This finding is largely unexplained but is speculated to relate to a genetic predisposition to T cell ALL in the male population (Jackson, Menon, Zarina, Zawawi & Naing, 1999). By contrast, there are no notable gender differences in the development of AML (Belson et al., 2007). In terms of race/ethnicity, while the highest incidence rates are observed amongst white European and American children (Belson et al., 2007), the lowest survival rates are seen amongst children of minority groups living in the USA: Black and Hispanic children have historically been associated with a poorer outcome and a lower survival rate for a number of social reasons, the most important being socioeconomic status (Bhatia et al., 2002). Minority groups in the USA tend to come from low socioeconomic backgrounds and often do not have ready access to quality health care. They also have fewer resources to maintain compliance with treatment

(Bhatia et al., 2002). This position greatly affects their treatment outcome, since all leukaemias are fatal without proper treatment (Marieb & Hoehn, 2014).

2.3 The South African Acute Leukaemia Situation

Botha and Kruger (2012) note that accurate statistical data for paediatric cancer in South Africa is not available, making it very difficult to adequately contextualise local studies on the topic and draw comparisons with the rest of the world. Statistical data pertaining to incidence is inaccurate due to the serious problems of under-diagnosis and under-reporting in South Africa (Albrecht, 2006). According to the national census conducted in 2011, approximately 16 million children constitute the paediatric population in South Africa (Statistics South Africa, 2012). Using this figure and applying the international incidence rate previously reported (14 children per 100 000), an estimated 2200 new paediatric oncology cases should be reported in South Africa every year. In reality, only 600 to 700 new cases have been reported each year for the last 25 years, which is less than one-third of the total number of children thought to be living with cancer in South Africa (Poyiadjis et al., 2011; Stefan & Stones, 2012). This discrepancy is related to factors such as a failure to diagnose cancer in children, delays in referrals to paediatric oncology units, and a failure to report new cases to the children's cancer registry (Stefan & Stones, 2012). A failure to diagnose cancer in South African children originates at the level of primary health care, which is inadequate in the rural areas of South Africa (Poyiadjis et al., 2011). The failure of primary health care workers to detect cancer in children has resulted in early deaths in two-thirds of children living with cancer in South Africa (Poyiadjis et al., 2011). Delays in patient referrals also originate at the level of primary health care,

since primary health care workers are responsible for referring children to specialist paediatric oncology units in South Africa (Poyiadjis et al., 2011). A failure to report new cases to the cancer registry, however, originates at the level of large tertiary hospitals, which are overwhelmed by administrative issues (Stefan & Stones, 2012). All of these issues contribute to the seemingly lower incidence rates of paediatric leukaemia in South Africa in comparison to the rest of the world.

As a supplement to the cancer registries, the researcher searched the local literature in the field of paediatric leukaemia for accurate data. A limited amount of resources has been allocated to paediatric leukaemia research in South Africa because the Department of Health has prioritised other pressing health problems such as HIV/AIDS, malaria and tuberculosis (American Cancer Society, 2011). One study, however, by Poyiadjis and colleagues (2011), proved to be very helpful and was relied upon heavily in respect of contextualising acute leukaemia in South Africa. In the following section addressing the epidemiology of acute leukaemia in South Africa, the statistics that have been reported should be interpreted with care. While the researcher acknowledges that some of the information provided might be outdated, every effort was made to provide the most current available information.

According to Stefan and Stones (2012), the South African Children's Tumour Registry (SACTR) is currently the main source of statistical data for epidemiological studies in the paediatric oncology field in South Africa. The SACTR is responsible for the recording of reported cases on an ongoing basis; however, due to delays in data capturing, only a small section of the registry has been published (Stefan & Stones, 2012). Table 1 below presents the number of registered leukaemia cases in the

SACTR from 1997 to 2007; the most recently published results (Stefan & Stones, 2012).

Table 1

Number of South African Children Diagnosed with Leukaemia, 1997-2007

1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
146	157	142	177	162	140	162	206	154	139	150	1737

It is important to realise that Table 1 above reflects only diagnosed and reported incidences. It does not take into account those children who die undiagnosed at home or at outlying hospitals (Poyiadjis, Wainwright, Naidu, Mackinnon & Mdluli, 2004). It also does not account for unreported cases. In order to provide a better idea of what the leukaemia incidence rates in Table 1 should look like, the researcher applied the international statistics (3 to 4 cases of ALL per 100 000 children and 0.5 cases of AML per 100 000 children) to the 15 million children that were living in South Africa in 2001 (Statistics South Africa, 2003). An estimated 600 new paediatric leukaemia cases should have been reported in 2001, which is approximately four times as many as were actually reported. It is important to understand that while the South African incidence rates are seemingly lower than the international incidence rates, there is a strong probability that this is due to the issues of under-diagnosis and under-reporting, rather than to a genuinely lower risk (Stiller & Parkin, 1996).

According to Statistics South Africa (2014), approximately 45,5% of the South African population resides in low socioeconomic rural areas, where poverty levels are high and access to modern health care facilities is limited. As a result, traditional healers have become the established primary health care providers in rural

communities, with more than 60% of all healing taking place outside the formal western-styled health care system in South Africa (Semenya & Potgieter, 2014). Since most traditional healers have no or limited formal schooling background, their education levels are low (Semenya & Potgieter, 2014). As a result, acute leukaemia in rural children goes largely undetected, contributing to the high number of deaths before diagnosis in South Africa (Poyiadjis et al., 2011). Poor primary health care also accounts for the late presentation of children to specialist paediatric oncology units (Poyiadjis et al., 2011).

The fact that children generally present to a paediatric oncology unit in the advanced stage of disease is what makes leukaemia treatment in South Africa so challenging, often resulting in an unsuccessful outcome. This problem was realised in 1998, after a decade-long study was conducted in the paediatric oncology unit at the Chris Hani Baragwanath Academic Hospital to assess the time delay between first presentation of symptoms and arrival in the paediatric oncology unit (Poyiadjis et al., 2004). In this study, it was found that the average time delay between the initial complaint and diagnosis was 10.1 months (Poyiadjis et al., 2004). In the context of acute disease, 10.1 months is a very late presentation, coinciding with a survival rate of only 48% (Poyiadjis et al., 2011). These findings highlighted the importance of early diagnosis and treatment.

In the interest of early referral to a paediatric onocology unit, the South African Children's Cancer Study Group compiled the Saint Siluan warning signs of cancer in children (Poyiadjis et al., 2011). The Saint Siluan warning signs were developed to aid primary health care workers in the early detection of leukaemia, thereby hoping to

decrease late presentation and increase survival (Poyiadjis et al., 2011). The common clinical presentation of acute leukaemia can be difficult to differentiate from other childhood complaints and often leads to a misdiagnosis, which delays treatment and contributes to higher rates of late diagnosis (Cantrell & Ruble, 2011). To illustrate this point, some participants in the present study were initially misdiagnosed with malaria and mumps before receiving a proper diagnosis of acute leukaemia. The Saint Siluan warning signs are therefore intended to clearly delineate the signs and symptoms of the disease so that a cancer diagnosis is not missed. They can be recalled by the acronym SILUAN: S stands for "seek" medical attention early for persistent symptoms; I stands for "eye" and warns about a white spot in the eye, new squint, new blindness or bulging eyeball; L stands for "lump", which may be present in the abdomen and pelvis, head and neck, limbs, testes or glands; U stands for "unexplained" and includes a prolonged fever for more than 2 weeks, weight loss, pallor, fatigue, easy bruising or easy bleeding; A stands for "aching" and refers to bone pain, joint pain, and easy fractures; and N stands for "neurological signs" such as a change or deterioration in gait, balance or speech, regression of milestones, headaches for more than one week with or without vomiting, or an enlarging head (Poyiadjis et al., 2011).

Although the Saint Siluan warning signs have assisted primary health care providers in detecting cancer in children and have significantly increased the number of new patients referred to specialist paediatric oncology units in South Africa, they have not succeeded in early referrals (Poyiadjis et al., 2011). Patients continue to present late to specialist units and are diagnosed in the advanced stage of disease (Poyiadjis et al., 2011). This indicates that further educational campaigns are required in the rural areas

of South Africa in order to improve early diagnosis. Acting on this, CHOC formed a partnership with the Gauteng Department of Health in 2011 and commenced a 3 to 5 year childhood cancer awareness campaign with the intention of improving early diagnosis in South Africa. According to the latest report, the aim of this campaign is to train all primary health care providers in Gauteng (including traditional healers) in the Saint Siluan warning signs of cancer in children, and, most importantly, to provide primary health care workers with the tools for rapid referral to a recognised paediatric oncology unit (CHOC Childhood Cancer Foundation [Johannesburg Division] & Gauteng Department of Health, 2012). The efficacy of this 3 to 5 year educational awareness campaign is yet to be evaluated.

Now that the critical issue of late diagnosis has been addressed, the clinical, biological and socioeconomic factors that are unique to South African children with leukaemia must be addressed. In contrast to the developed world, where ALL is diagnosed four times more frequently than AML, ALL and AML are diagnosed with equal frequency in sub-Saharan Africa (Fleming, 1993). This is due to the relatively high incidence of AML in sub-Saharan Africa (Fleming, 1993). Central to this high incidence is socioeconomic status: For reasons that are unknown, AML has a pattern of affecting low socioeconomic children in South Africa (Fleming, 1993). Given that 45,5% of the South African population reside in rural areas and are of a low socioeconomic background (Statistics South Africa, 2014), this may explain the higher incidence of AML in South Africa relative to the developed world.

In terms of demographic risk factors in South Africa, acute leukaemia can occur in children of any age (Botha & Kruger, 2012). The peak incidence of 2 to 5 years of age

for ALL in the developed world is absent in sub-Saharan Africa, with ALL occurring anywhere between 5 and 14 years of age (Fleming, 1993; Stiller & Parkin, 1996). As with the international situation, males are more genetically predisposed to developing ALL (particularly T cell ALL) than females (Belson et al., 2007; Jackson, et al., 1999). In sub-Saharan Africa, the male to female ratio for ALL approaches 2:1 (Fleming, 1993). Since males have a higher incidence of T cell ALL (particularly black African males), they tend to have a worse prognosis than females due to resistant disease (American Cancer Society, 2013; Stiller & Parkin, 1996). Consequently, males may be prone to shorter survival. Male children are also four times more likely than female children to receive a diagnosis of AML (Fleming, 1993). The reason for this gender disparity is unclear but is speculated to be a genetic predisposition to AML in the male population (Jackson et al., 1999).

Since leukaemia is diagnosed across children of all races in South Africa, race/ethnicity does not seem to have an effect on its development (The Cancer Association of South Africa, 2014). Race/ethnicity does, however, have an effect on prognosis, with black African children demonstrating a constellation of clinical, biological and social factors associated with poor outcome (Fleming, 1993). Biologically and clinically, black African children have a high incidence of T cell ALL and AML (B. Goodwin, personal communication, March 5, 2014; Fleming, 1993; Stiller & Parkin, 1996). T cell ALL and AML are known to be the most resistant diseases, which is precisely why black children have the worst prognosis in South Africa (Fleming, 1993). In terms of social factors, black African children are at increased risk for late diagnosis due to the inadequacy of primary health care in rural areas and reduced access to large tertiary hospitals where leukaemia is treated (Byrne

et al., 2011; De Boer, Boellaard, Parkinson, Blanchard & Heij, 2009). Late diagnosis is associated with a low complete remission rate and short survival in black African children, who are also associated with poor compliance to treatment regimens due to a lack of parental education and long distances to travel for treatment (Byrne et al., 2011; De Boer et al., 2009; Fleming, 1993). A lack of education is the primary reason why many parents do not realise the medical urgency in treating acute leukaemia, and do not understand the importance of completing treatment (De Boer et al., 2009). Long distances between home and hospital means that patients do not always have the financial resources or transport to travel to hospital for treatment (De Boer et al., 2009). Poor compliance poses a serious threat to treatment outcome because the treatment protocols have been carefully designed to prescribe specific therapies at specific times to ensure an optimal outcome. Patients who do not comply with these instructions do not receive the benefit of protocol-based therapy. It is for this reason that doctors continually emphasise the importance of treatment compliance to parents, especially those with no or little education (De Boer et al., 2009). In the context of rural South Africa, this is often much more complex than it seems and requires multiple conversations throughout the course of treatment. Many patients reside in Johannesburg with extended family members while they are receiving treatment. These patients often travel back to their hometowns during the school holidays, without fully appreciating the consequences of their medication depleting during this time. Upon returning to hospital, doctors may have to manage the fact that patients have not been taking their prescribed medication, which is one of the complications of treatment in South Africa. Western medicine also has to contend with traditional medicine in rural South Africa (Semenya & Potgieter, 2014). Some children may abandon treatment and opt for a traditional healing approach, particularly when the

adverse side effects of treatment convince poorly educated parents/caregivers that continuing with treatment is not in the best interests of the child (De Boer et al., 2009). All of these social factors can complicate treatment in black African children, leading to a less than favourable outcome.

In summary, the South African situation differs in many respects from that of the developed world. These differences are not attributable to inadequate leukaemia treatment but rather to the unique social, clinical and biological factors surrounding low socioeconomic rural children in South Africa, who most often present in the advanced stage of disease and do not always maintain compliance with treatment.

2.4 Acute Leukaemia Treatment in South Africa

In South Africa, paediatric acute leukaemia is treated in specialist units in large academic teaching hospitals in the public sector (CHOC, 2014b). As mentioned previously, a multidisciplinary approach is adopted in these units, which follow well-established international treatment protocols, namely the Berlin-Frankfurt-Münster (BFM) protocols.

The BFM protocols are among the most commonly used protocols in the world (Wetzler, 2012). They were developed in Germany in 1975, and various protocol modifications have been made over the years to improve treatment efficacy (International BFM Study Group, 2014). The cornerstone of the BFM protocols is "risk-adapted treatment", which allows paediatric oncologists to tailor patients' treatment regimens according to important prognostic factors, such as age at diagnosis

and initial response to treatment (ENCCA, 2013; Meshinchi & Arceci, 2007). In comparing the BFM protocols to other international leukaemia treatment protocols, it is precisely this risk-adapted treatment that makes the BFM protocols so effective (ENCCA, 2013).

Before the BFM protocols for ALL and AML are discussed in greater detail, it must be emphasised that these protocols have undergone modifications over the years as clinicians have worked to design protocols that adequately treat acute leukaemia with minimal impact on cognitive function (Cantrell & Ruble, 2011). One of the major modifications has been the introduction of high-dose methotrexate (an intensive antileukaemic drug), and a reduction in the dose of radiation delivered to the brain (Möricke et al., 2008). This is a highly relevant modification in the context of this study. It means that cranial irradiation is currently administered at prudent doses, but the findings of this study will help determine whether a degree of cognitive impairment still exists at these currently prescribed doses.

2.4.1 ALL-BFM 95

This is the treatment protocol followed for patients with an ALL diagnosis. It comprises five treatment phases, namely induction, consolidation, CNS intensification, reinduction-reintensification, and maintenance. The induction phase is the first phase of treatment and is critical for determining the patients' initial response to treatment. The aim of induction is to achieve complete remission within 4 to 6 weeks, using a combination of chemotherapeutic drugs (ENCCA, 2013). The next two treatment phases, consolidation and intensification, are aimed at killing any residual leukaemic blasts that may be in the blood and bone marrow (ENCCA, 2013).

These phases are important in preventing bone marrow relapse (ENCCA, 2013). Intensification is the third phase of treatment in which cranial irradiation is administered to prevent CNS relapse (the reader is referred to the heading "CNS prophylaxis" below for a further discussion). The final phase of treatment is known as maintenance. It begins approximately 6 months after diagnosis and lasts approximately 2.5 years. This brings the total treatment time for ALL to 3 years. The purpose of maintenance is to stabilise remission and prevent relapse by administering lower doses of chemotherapy over a prolonged period of time (ENCCA, 2013).

2.4.2 AML-BFM 98

This is the treatment protocol followed for patients with an AML diagnosis. It is rather different from the ALL-BFM 95 in that children with AML are treated with more aggressive chemotherapy over a shorter period of time (Leung et al., 2000). The AML-BFM 98 comprises four to six treatment phases, with the standard phases being induction, consolidation, intensification, and maintenance (Gibson, Perentesis, Alonzo & Kaspers, 2011). Induction in AML is aimed at complete remission within the first 2 to 3 weeks, using a combination of antileukaemic drugs (ENCCA, 2013). Consolidation and intensification are similar to that of ALL in that they are aimed at eliminating any residual leukaemic cells in the blood and bone marrow following induction (ENCCA, 2013). Unlike ALL, however, cranial irradiation is administered at the beginning of the maintenance phase, which is the final phase of AML treatment. Maintenance commences approximately 6 months after diagnosis and lasts one year. This brings the total treatment time for AML to 1.5 years (ENCCA, 2013). As with ALL, the purpose of maintenance is to ensure that the leukaemia does not

return by administering lower doses of chemotherapy over a prolonged period of time (ENCCA, 2013).

2.4.3 CNS prophylaxis

The BFM protocols described above prescribe CNS-directed therapy either during intensification (ALL) or during maintenance (AML) to prevent CNS relapse (ENCCA, 2013). Central nervous system prophylaxis involves the regular administration of intrathecal chemotherapy throughout the course of treatment, as well as the administration of 12 or 18 Gy of cranial irradiation at a specified stage in the treatment process (National Cancer Institute, 2014a).

The term "intrathecal" refers to the route of administration of chemotherapy, which is injected via a lumbar puncture into the subarachnoid space of the spinal cord, the area containing the cerebrospinal fluid. Intrathecal administration allows the drugs to penetrate the CNS directly, thereby avoiding the blood-brain barrier that is encountered by traditional "systemic" chemotherapy, which is administered intravenously. At this point, it is important to acknowledge the possible effects of chemotherapy on cognitive functioning. Given that the blood-brain barrier restricts direct entry of antileukaemic drugs to the brain, systemic chemotherapy has little (if any) effect on cognitive functions (Giordano et al., 2012). However, when the blood-brain barrier is bypassed by intrathecal chemotherapy, one has to consider the possibility that cognitive functioning may be affected. Research into the cognitive effects of intrathecal chemotherapy alone has not consistently yielded any conclusive findings (Raymond-Speden, Tripp, Lawrence & Holdaway, 2000). Some studies have failed to find any evidence of cognitive impairment, while other studies have reported

mild cognitive deficits, primarily in the domain of verbal memory (Daams et al., 2012; Raymond-Speden et al., 2000; Roberts, Seropian & Marks, 2013). Therefore, if verbal memory deficits are identified in the present study, the impact of intrathecal chemotherapy will need to be considered in addition to the impact of cranial irradiation. Daams and colleagues (2012) acknowledge, however, that the cognitive effects emanating from intrathecal chemotherapy alone are subtle in comparison to those emanating from cranial irradiation.

Cranial irradiation is generally a prerequisite for the successful treatment of acute leukaemia, as it is highly effective in preventing CNS relapse (ENCCA, 2013; Hata et al., 2001). Children with an ALL diagnosis are treated with cranial irradiation provided that they are 6 years or older at the time of diagnosis (Roberts et al., 2013). Older children undergo cranial irradiation because they are often associated with T cell ALL and tend to have a poorer prognosis than younger children (ENCCA, 2013; Fleming, 1993). Younger children with ALL tend to have a high success rate with chemotherapy alone, and in an effort to spare the young brain from harm, cranial irradiation is avoided in children below the age of 6, and high-dose methotrexate is given instead (B. Goodwin, personal communication, March 5, 2014). By contrast, cranial irradiation is given to children of all ages with AML, as all ages have an equally poor prognosis (Meshinchi & Arceci, 2007). Unfortunately, this has serious negative implications for younger patients, whose brains are at a critical stage of development when they undergo cranial irradiation. The irradiation procedure is the same for children with ALL and AML. Typically, the whole skull is irradiated, up to and including the second cervical vertebra (Marsh, Gielda, Herskovic & Abrams, 2010). Depending on the dosage deemed suitable for the child, this is either done in 8

daily fractions of 1.5 Gy to total 12 Gy, or in 10 daily fractions of 1.8 Gy to total 18 Gy.

2.4.4 Potential for pre-treatment cognitive deficits

This study focuses on cognitive deficits relating to treatment effects. At this point, it is important to consider whether children with acute leukaemia may have pre-existing cognitive deficits prior to the commencement of treatment. The Saint Siluan warning signs, which have already been discussed, mostly resemble common flu-like symptoms. However, special attention needs to be drawn to the N warning sign, which refers to neurological signs. The fact that neurological signs may be present before treatment suggests that neurological deterioration may be part of the disease process itself, particularly in cases where the leukaemia has spread to the CNS. The presence of neurological signs at diagnosis is characteristic of advanced stage disease (National Cancer Institute, 2014a). Although little is known about the impact of the actual disease process on cognition (because children with acute leukaemia do not survive long without treatment), it is more than likely that children with CNS disease at diagnosis have pre-existing cognitive deficits. This was an important consideration for this study, as the presence of pre-existing cognitive deficits may have introduced a confounding variable into the results. Fortunately, none of the participants in this study had CNS disease at diagnosis, eliminating the potential for pre-treatment cognitive deficits in respect of disease processes. Moreover, all the participants in this study had received or were receiving CNS prophylaxis during their treatment, which controlled for the possibility of CNS relapse. As such, any cognitive deficits identified in the present study can be potentially attributed to treatment toxicities.

PART II: Neuropsychological Functioning

2.5 Overview of Brain Structure and Function

In order to fully understand the mechanisms of information processing in the brain, it is first necessary to understand how the brain develops and why it is organised in the way it is. Cortical organisation is of critical importance because information processing requires the integration of information from different regions in the brain. While the resulting cognitive experience is more than the sum of the isolated elements in the information processing system, the elements must be explained before the process of integration can be fully understood (Strauss, Sherman & Spreen, 2006).

2.5.1 Brain development

Brain development occurs from the inside out and from back to front, beginning with the formation of deep subcortical structures and extending to the outermost layer of the brain, the cerebral cortex (Gazzaniga, Ivry & Mangun, 2009). While the outermost cerebral cortex is composed of grey matter (collections of nerve cell bodies), the deeper part of the brain is composed mostly of white matter (bundles of myelinated axons) (Gazzaniga et al., 2009). There are, however, islands of grey matter scattered within the deep cerebral white matter, which are known as subcortical structures. The subcortical structures include the basal ganglia and the brain stem nuclei (Marieb & Hoehn, 2014). While grey matter is associated with processing and cognition (particularly language and declarative memory), white matter plays a critical role in providing the structural and functional connections between grey matter areas within the brain, and is therefore involved in coordinating communication between different

brain regions (Anderson et al., 2008; Filley, 2005). In terms of cognition, white matter plays a critical role in speed of information processing, sustained attention, and visuospatial tasks (Anderson et al., 2008).

2.5.2 Cortical organisation and hemispheric specialisation

The cerebral cortex is the most highly organised area of the brain (Lezak, Howieson, Bigler & Tranel, 2012). Structurally, it is organised into two cerebral hemispheres, with each hemisphere further sub-divided into four major lobes (Lezak et al., 2012).

The longitudinal fissure, which runs anteriorly to posteriorly down the centre of the brain, divides the cortex into two approximately symmetrical and equal hemispheres (Lezak et al., 2012). The right and left hemispheres are specialised for different cognitive functions. This is the premise of the theory of hemispheric specialisation, which states that, in most cases, the left hemisphere processes verbal information, and the right hemisphere processes visuospatial information (Lezak et al., 2012). This means that the left hemisphere is primarily responsible for cognitive tasks involving reading, writing, verbal comprehension, spoken language, and verbal memory; whereas the right hemisphere is primarily responsible for cognitive tasks involving spatial perception, tactile and visual recognition of shapes and objects, as well as copying and drawing designs, patterns and pictures (Lezak et al., 2012).

Perhaps some of the most well known figures in the study of hemispheric specialisation are Paul Broca (1861) and Carl Wernicke (1874), who localised speech production and comprehension to specific and distinct areas in the left hemisphere (Lezak et al., 2012). In a similar way, researchers investigating facial recognition

localised facial processing to the right hemisphere upon finding that pictured faces were processed more rapidly by the right hemisphere than by the left (Lezak et al., 2012). In later years, Roger Sperry (1968), who conducted split-brain research on epileptic patients, suggested that the two hemispheres functioned like separate brains (Gazzaniga et al., 2009). After severing the corpus callosum, the white matter commissure connecting the two hemispheres, Sperry found that information presented to one hemisphere went unnoticed by the other (Gazzaniga et al., 2009). Sperry was thus able to observe the functioning of each hemisphere in isolation, confirming that the left hemisphere was responsible for verbal and analytical processing, and the right hemisphere was responsible for visuospatial and holistic processing (Gazzaniga et al., 2009). Although a useful theory in its time, today this view is an oversimplification and, in fact, the two hemispheres work together in almost all aspects of brain functioning (Gazzaniga et al., 2009).

The four major lobes comprising each hemisphere are the frontal, parietal, occipital and temporal lobes. Each lobe contains distinct structures that are specialised for different functions (Gazzaniga et al., 2009). The major lobes and their structural-functional relationships are discussed below.

The frontal lobe lies anterior to the central sulcus, a deep groove separating the frontal and parietal lobes (Gazzaniga et al., 2009). The frontal lobe is the largest lobe in the fully developed brain. It the last area of the brain to develop, reaching its maximum thickness by age 11 in females and 12.1 in males (Samango-Sprouse, 2007). The frontal lobe is the seat of higher cognitive functions in the brain (Gazzaniga et al., 2009). It contains an important region called the prefrontal cortex, which is located in

the anteriormost part of the frontal lobe and mediates executive functions (Lezak et al., 2012).

The prefrontal cortex is the very last area of the frontal lobe to mature, and is not fully developed until the age of 25 (Samango-Sprouse, 2007). The three major areas within the prefrontal cortex are the ventromedial prefrontal cortex, the dorsolateral prefrontal cortex, and the medial prefrontal cortex (Lezak et al., 2012). The ventromedial prefrontal cortex plays a key role in impulse control and in regulating and maintaining ongoing behaviour (Lezak et al., 2012). Damage to this area typically results in impulsivity and disinhibition, the signs of which include a lack of planning, poor judgment, and inappropriate social behaviour (Lezak et al., 2012). The dorsolateral prefrontal cortex is involved in higher order cognitive functions, with its major function being working memory (Lezak et al., 2012). The left dorsolateral prefrontal cortex is involved in verbal working memory, and the right dorsolateral prefrontal cortex is involved in visuospatial working memory (Lezak et al., 2012). Another important function of the dorsolateral prefrontal cortex is the organisation of information in memory, which depends on the strategies contributed by the prefrontal cortex when new information is learnt (Lum, Conti-Ramsden, Page & Ullman, 2012). Organisational strategies differ in the verbal and visuospatial domains and are discussed in more detail when the tests of verbal and visuospatial memory are discussed in the next chapter. Evidence also suggests that the dorsolateral prefrontal cortex plays a key role in intelligence by contributing appropriate problem solving strategies to complex cognitive tasks (Lezak et al., 2012). Finally, the medial prefrontal cortex houses the anterior cingulate cortex, which is an important structure involved in self-monitoring behaviour and enhancing attentional processes (Lezak et

al., 2012). It is therefore clear that the main functions of the prefrontal cortex are the executive functions of planning, organisation, attention and working memory.

The parietal lobe is located posterior to the central sulcus and matures in the first two years of childhood (Samango-Sprouse, 2007). The neural connections between the parietal lobe and the hypothalamus allow the parietal lobe to play a supporting role in working memory (Lum et al., 2012). Specifically, the left parietal lobe supports verbal working memory and the right parietal lobe supports visuospatial working memory (Devinsky & D'Esposito, 2004; Lum et al., 2012).

Sack and colleagues (2002) posit that the parietal cortex is also the site of visuospatial processing in the brain. Visuospatial processing involves the abilities of visual perception, spatial orientation and visual attention, and is highly dependent on the right hemisphere (Lezak et al., 2012). Deficits in visuospatial processing are observed in individuals who experience difficulty with visual orientation of lines and patterns, geometric block design and assembly, and drawing complex figures (Devinsky & D'Esposito, 2004). While the right parietal lobe mediates visual perception and the overall gestalt, the left parietal lobe is concerned with visual detail (Devinsky & D'Esposito, 2004). It follows that lesions in the right parietal lobe impair the ability to integrate parts into a consistent whole, whereas lesions in the left parietal lobe impair the ability to perceive visual detail (Devinsky & D'Esposito, 2004). Because the parietal lobe is involved in visuospatial processing, it is intimately connected to the occipital lobe, which provides visual sensory input, and to the temporal lobe, which provides spatial memory (Raber, 2010). It also relies heavily on the prefrontal cortex for attentional control in visuospatial tasks (Silk et al., 2006).

The occipital lobe is located at the back of the brain, behind the parietal and temporal lobes (Gazzaniga et al., 2009). It houses the primary visual cortex, which matures in the first two years of childhood (Samango-Sprouse, 2007). The primary visual cortex analyses incoming visual information in terms of its basic qualities such as colour, shape and size (Gazzaniga et al., 2009). Although the occipital lobe is the site of vision in the brain, it is important to appreciate that complex visual information processing also involves the parietal and temporal lobes: Visual sensory input is interpreted by the primary visual cortex in the occipital lobe, integrated with visuospatial information in the parietal lobe and with spatial memory in the temporal lobe, and finally a complete visual representation of the object is formed. This is one such demonstration of the vast amount of integration that occurs in the brain.

The temporal lobe lies below the Sylvian fissure, which separates the temporal lobe from the frontal and parietal lobes (Gazzaniga et al., 2009). In terms of cognition, the temporal lobe functions in long-term memory. It houses the medial temporal lobe, which is an important region for memory. Lesions in the left medial temporal lobe tend to disrupt verbal learning and memory, and lesions in the right medial temporal lobe disrupt visuospatial learning and memory (Lezak et al., 2012). The hippocampus is one of the critical subcortical structures located in the medial temporal lobe, and is responsible for consolidating new memories (Lezak et al., 2012). Lesions in the hippocampus result in the inability to learn new information throughout life (Marsh et al., 2010). The hippocampus usually works together with the prefrontal cortex, which plays an important role in working memory (Lezak et al., 2012). Later, it will be seen how working memory and long-term memory work together to encode, store and

retrieve information. The hippocampus also works closely with the right parietal lobe in visuospatial processing, since the hippocampus is responsible for providing spatial memory in visuospatial tasks (Raber, 2010).

2.5.3 Luria's hierarchical model of cortical functioning

Although the theory of hemispheric specialisation helped to separate out the functional differences between the two cerebral hemispheres, Sperry's findings proved that the connectivity between the different regions of the brain was just as important, if not more important, than the operations of the isolated regions themselves (Lezak et al., 2012). This is because, without directly damaging either hemisphere, Sperry was able to cause pervasive cognitive loss merely by severing the structure that connected the two hemispheres, the corpus callosum. In response to this, the integrationist approach to brain functioning was born.

Alexandra Luria (1970) was a Russian neuropsychologist who was very much against a localisationist view of the brain and came to develop a theory based on the functional systems in the brain. Luria's hierarchical model of cortical functioning provides a rich neuropsychological framework, which proposes that while different areas of the brain are specialised for different functions, these specialised functions are not sufficient on their own to produce complex behaviour (Andrewes, 2001). Functional systems, such as those involved in cognitive processes, require a complex interaction of different brain regions, with each brain region performing a different specialised function (Andrewes, 2001). Andrewes (2001) uses the metaphor of an orchestra to describe Luria's model, and explains that just as a complete symphony is dependent on the coordinated product of different sections of the orchestra, so too is

the overall cognitive experience dependent on the coordinated product of different regions of the brain.

Luria divided the brain into three anatomical and functional units: the lower, posterior and frontal regions. The lower region of the brain includes the brain stem and the thalamus (Andrewes, 2001). The reticular formation in the brain stem is responsible for regulating alertness and the thalamus is responsible for relaying sensory information to higher cortical areas (Marieb & Hoehn, 2014). The purpose of the lower functional unit is to provide an optimal level of brain arousal in order to carry out cognitive functions (Andrewes, 2001). The posterior part of the brain is the unit that analyses and stores newly received information (Andrewes, 2001). This unit includes the primary somatosensory cortex of the parietal lobe, the primary visual cortex of the occipital lobe, the primary auditory cortex of the temporal lobe, as well as the association areas of the brain (Andrewes, 2001). Basic sensory input flows to the appropriate primary sensory area, then to a sensory association cortex, then on to the multimodal association cortex, which gives meaning to the information we receive, and allows us to store it in memory, compare it to existing experience and knowledge, and decide on an appropriate action (Marieb & Hoehn, 2014). Finally, the frontal region of the brain is responsible for directing and controlling all other mental activities (Andrewes, 2001). It formulates plans, strategies and actions, controls behaviour, coordinates problem solving, inhibits impulse, and self monitors behaviour (Pohlman, 2008). Metaphorically speaking, the frontal region acts as the conductor of the orchestra (Pohlman, 2008).

In summary, Luria's qualitative approach to brain functioning acknowledges specialisation but also highlights the interdependence between the specialised brain regions. The three functional units discussed above, one providing arousal, one allowing for the analysis of incoming information, and one producing and organising behaviour, are dependent on one other and must work together to produce complex behaviour (Andrewes, 2001).

2.5.4 Importance of white matter tracts in functional systems

White matter tracts, which provide cortical-cortical and cortical-subcortical connections, play a critical role in integrating information into functional systems in the brain (Filley, 2005). Two neuropsychological functions that are highly dependent on these white matter tracts are processing speed and visuospatial processing, because they require a large amount of integration from different sources of information in the brain (Anderson et al., 2008). A prime example of two functional systems working together is the fronto-parietal network, which consists of the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the parietal lobes (Brinkman et al., 2012). The fronto-parietal network supports the integration and control of executive functions in the brain (Brinkman et al., 2012) and is responsible for attentional control in respect of visuospatial tasks (Silk et al., 2006). The integration of information between the frontal and parietal lobes is a central theme in this study, and the fronto-parietal network will be referred to again at various points in this paper.

2.6 Major Domains of Neuropsychological Functioning

Neuropsychological functioning has been divided into a number of functional domains, namely intellectual functioning, executive functions (attention, working memory, and processing speed), memory and learning, and social-emotional functioning. These domains are discussed in more detail below.

2.6.1 Intellectual functioning

The concept of intelligence has been a complex topic in the field of psychology, with some theorists (e.g. Charles Spearman) believing in a single general intelligence, and other theorists (e.g. Howard Gardner) believing in the idea of multiple intelligences (Strauss et al., 2006). Supporters of the general intelligence theory believe that a single general ability underlies all cognitive activities, and this single ability is what Spearman termed the *g* factor (Strauss et al., 2006). What is problematic about Spearman's *g* is that if it were compromised in some way, all aspects of cognitive functioning would be impaired. Two pieces of evidence demonstrate that this is not necessarily the case: Firstly, brain lesions, and brain damage in the broader sense, can disrupt some cognitive functions while sparing others; and secondly, the cognitive functions that are affected tend to decline at different rates (Lezak et al., 2012). In the interest of refining the theory of general intelligence, Raymond Cattel (1971) distinguished between two components of general intelligence, namely fluid and crystallised intelligence (Strauss et al., 2006). Fluid intelligence refers to the ability to solve problems without any prior knowledge or experience (Lezak et al., 2012). It has been linked to the dorsolateral prefrontal cortex because working memory plays a key role in fluid intelligence (Lezak et al., 2012). Crystallised intelligence, on the other

hand, involves the solving of problems based on acquired knowledge (Lezak et al., 2012). It has been linked to the hippocampus because long-term memory plays an important role in crystallised intelligence (Nairne, 2009). Cattel suggested that an individual draws on both components of intelligence, such that problem solving ability (fluid intelligence) is largely dependent on past experiences with similar problems (crystallised intelligence).

Supporters of the multiple intelligences theory believe that individuals have a variety of different intelligences. As such, different cognitive domains are involved in different types of problem solving tasks. This is in line with David Wechsler's view of intelligence, which is the view that intelligence is multi-determined and multi-faceted. As a result, the Wechsler intelligence tests encompass many different cognitive functions. Moreover, Wechsler recognised the role of the frontal lobes in human intelligence, and he also include executive functions such as attention and processing speed in his intelligence tests (Lezak et al., 2012). The view that there are various cognitive domains involved in intelligence, and that these domains operate somewhat independently from one another, seems to provide an adequate explanation for why certain cognitive functions can be damaged by neurological insults while others can remain relatively intact (Strauss et al., 2006).

Modern theorists of intelligence have relied on factor analytic research methods to further investigate the concept of intelligence. The results have implicated several higher-level abilities, as well as a number of lower-level abilities, in the concept of intelligence (Strauss et al., 2006). Higher-level abilities include fluid and crystallised intelligence, short-term memory, long-term memory, and processing speed; while

lower-level abilities include numerical reasoning, spelling, and reaction time (Strauss et al., 2006).

Lezak and colleagues (2012) caution that, given what we know today about the complexities of brain organisation and brain dysfunction, a unitary concept of intelligence is irrelevant and misleading. The term "intelligence quotient (IQ)" is tied to the idea that intelligence is a unitary concept, yet the various tasks from which intelligence tests are composed represent so many different types of cognitive functions, making the score conceptually meaningless (Lezak et al., 2012). Rather than assigning meaning to the IQ score itself, the analysis of the performance profile provided by intelligence subtests is of far greater importance. This is particularly important in neuropsychological assessment, where the derived IQ score on its own may obscure selective defects in specific tasks (Lezak et al., 2012).

2.6.2 Executive functions

Executive functions, which rely on frontal lobe functioning, are a collection of mental activities involved in the control of higher-order cognitive functions (Logue & Gould, 2013). While executive function is often regarded as a unitary construct, it can also be conceptualised as involving a number of loosely-related functions that control cognitive performance (McCabe, Roediger, McDaniel, Balota & Hambrick, 2010). McCabe and colleagues (2010) suggest a middle-ground approach, one which characterises executive function as having both shared and distinct components. The shared component relates to a common executive attention factor underlying all tasks of executive function; while the distinct executive functions refer to any specific cognitive processes that are not shared by all executive function tasks, such as shifting

or inhibition (McCabe et al., 2010). This middle-ground approach was adopted in this study, as it allowed for the most inclusive assessment of executive functioning.

In the subsections below, three of the most important mental activities involved in executive functioning are discussed, namely attention, processing speed, and working memory (Logue & Gould, 2013). While it is important to understand that executive functions are a distinct class of functions from intellectual functions, they play an important role in intelligent behaviour by contributing effective planning and problem solving strategies to complex cognitive tasks (Lezak et al., 2012; Logue & Gould, 2013).

2.6.2.1 Attention

Attention is a fundamentally important mental activity because it underlies and maintains performance on all cognitive tasks (Lezak et al., 2012). Attention is focused and well sustained when the right prefrontal cortex is intact (Lezak et al., 2012; Samango-Sprouse, 2007). The basic functional form of attention is sustained attention, which allows individuals to maintain focus on a set of stimuli over a prolonged period of time (Sarter, Givens & Bruno, 2001). Silver and Feldman (2005) note that lesions in the prefrontal cortex, particularly in the regions of the right hemispheric anterior cingulate cortex and the dorsolateral prefrontal cortex, have a detrimental effect on sustained attention. Neuroimaging studies have also implicated the right parietal lobe in sustained attention, possibly because of its supporting role in working memory (Silver & Feldman, 2005). With sustained attention being the basic functional form of attention, it plays an important role in the quality and efficacy of higher levels of attention, such as selective and divided attention (Sarter et al., 2001).

Selective attention refers to the ability to maintain focus on a single set of stimuli while ignoring distractors (Gazzaniga et al., 2009). Divided attention is the process that occurs when two complex tasks, both of which require sustained attention, must be performed at the same time (Gazzaniga et al., 2009). Given that the capacity for sustained attention is limited, performance generally declines on one of the two tasks as they compete for cognitive resources (Gazzaniga et al., 2009).

2.6.2.2 Speed of information processing

The speed at which individuals process information is believed to constrain performance on all cognitive tasks, as slow processing limits the amount of information that is available for processing (McCabe et al., 2010). As mentioned previously, processing speed depends on the integrity of white matter tracts in the brain. Genova, DeLuca, Chiaravallotti and Wylie (2013) conducted a study on multiple sclerosis, which, like cranial irradiation, is characterised by white matter changes. They found that slow processing is a key factor contributing to poor performance on timed cognitive tasks. The link provided between white matter integrity and processing speed also highlights the importance of connectivity in the brain, particularly with respect to the rate at which individuals complete cognitive tasks (Dockstander et al., 2013). It follows that individuals with white matter damage are expected to exhibit processing speed deficits, which can be readily identified in cognitive tests that require speeded performance.

2.6.2.3 Working memory

Working memory refers to the ability to maintain information in mind for a matter of seconds, while performing mental manipulations on it (Lum et al., 2012). It differs

from short-term memory in that the information contained in working memory is manipulated and processed, rather than merely maintained through rehearsal (Gazzaniga et al., 2009). According to Baddeley and Hitch's (1974) model, working memory is composed of two subsystems: (a) the phonological loop, which temporarily stores verbal information, and (b) the visuospatial sketchpad, which temporarily stores visuospatial information (Lezak et al., 2012). Baddeley and Hitch also described a role for attention in working memory, including in their model an attentional control mechanism called the central executive, which focuses attention and regulates the flow of information into the phonological loop and visuospatial sketchpad (Lum et al., 2012).

The anatomical correlate of working memory is the dorsolateral prefrontal cortex, which plays an important role in the central executive and attentional processes (Lum et al., 2012). Specifically, the left dorsolateral prefrontal cortex is associated with verbal working memory (the phonological loop), while the right dorsolateral prefrontal cortex is associated with visuospatial working memory (the visuospatial sketchpad) (Lezak et al., 2012). As mentioned previously, the parietal lobe seems to play a supporting role in working memory, with the left parietal lobe involved in the temporary storage of verbal information, and the right parietal lobe involved in the temporary storage of visuospatial information (Lum et al., 2012).

Since sustained attention and the central executive share the same underlying neural mechanism, namely the prefrontal cortex, sustained attention and working memory are two interdependent cognitive processes (Silver & Feldman, 2005). This speaks to the shared component of executive functioning described by McCabe and colleagues

(2010). As such, tests of sustained attention and working memory may indeed measure the same construct (Silver & Feldman, 2005). It is therefore suspected that where sustained attention deficits are identified, working memory deficits may also be identified.

In addition to sustained attention, tests of working memory typically involve some form of mental double-tracking (Lezak et al., 2012). A breakdown in mental double-tracking is a common complaint after brain injury, and is experienced as a difficulty holding two or more trains of thought in mind at the same time (Lezak et al., 2012). A reduced capacity for mental double-tracking poses further limitations on the already limited capacity for divided attention, which is why problems with working memory and divided attention tend to co-occur.

2.6.3 Memory and learning

The long-term memory system involved in memories for facts and events is declarative memory (Gazzaniga et al., 2009). An important interaction between working memory and declarative memory takes place during the transfer of information out of temporary storage and into long-term storage, and then back into temporary storage when the information is required (Deluca & Chiaravalloti, 2004). This process is described in greater detail below.

Declarative memory underlies encoding, consolidation, storage and retrieval of semantic information (Lum et al., 2012). Semantic knowledge is the general knowledge an individual acquires about the world through learning (Lezak et al., 2012). Encoding, consolidation, storage and retrieval refer to the successive stages of

memory processing involved in the transfer of information from working memory to long-term memory. Encoding entails the rehearsing and processing of new incoming information, which occurs in working memory (Deluca & Chiaravalloti, 2004). As such, the dorsolateral prefrontal cortex plays a critical role in encoding (Deluca & Chiaravalloti, 2004). The improper functioning of the dorsolateral prefrontal cortex prevents new information from being encoded in working memory, making it difficult to learn new information effectively (Filley, 2005). When the prefrontal cortex is intact, new information is transferred out of the temporary store of working memory and into the long-term store of declarative memory through a process called consolidation (Deluca & Chiaravalloti, 2004). The hippocampus, which is located in the medial temporal lobe, plays a critical role in consolidation (Deluca & Chiaravalloti, 2004). The improper functioning of the hippocampus prevents new information from being consolidated in long-term memory. As a result, the information remains in temporary storage and decays after a few seconds. However, when the hippocampus is functioning properly, the new information is consolidated in long-term memory and stored on a more permanent basis. The process from encoding in working memory to consolidation in long-term memory is referred to as learning (Deluca & Chiaravalloti, 2004). Evidently, learning is highly dependent on the intact functioning of the memory system. The final phase of memory processing, retrieval, involves the use of this newly acquired semantic knowledge (Lum et al., 2012). It involves taking information out of long-term storage and transferring it back into working memory so that it may be manipulated for a purpose (Deluca & Chiaravalloti, 2004). The prefrontal cortex seems to be active again during the retrieval stage because retrieval essentially involves the re-encoding of information in working memory (Deluca & Chiaravalloti, 2004; Lum et al., 2012). When an

individual experiences problems with long-term memory, the deficit usually originates in one of the aforementioned stages of memory processing (encoding, consolidation, storage or retrieval), rather than in the memory system as a whole (Lezak et al., 2012). However, because the stages represent successive steps in a greater process, problems at the level of encoding are generally seen to affect the whole memory system.

2.6.4 Social-emotional functioning

Lezak and colleagues (2012) claim that structural changes in the brain can result in changes in personality, mood and emotions. In the context of children with leukaemia, psychological distress is common during the first few months of treatment, when children are highly stressed or fatigued (Fobair, 2007). Mood changes can also be an acute side effect of medication, for example, prednisone is a cortisone drug used in leukaemia treatment and is commonly associated with irritability. Cranial irradiation is also known to have an effect on emotion regulation, as structural changes in the frontal lobe may result in a weakened capacity for executive control. It is speculated that this may occur by disrupting the connectivity between the frontal lobes and the subcortical limbic system, which is responsible for regulating emotional states (Marsh et al., 2010). More permanent changes in mood and affect have been reported by some survivors in response to the troubling cognitive changes they experience after treatment, which lead to increased feelings of frustration (Fobair, 2007). It was therefore important to include a psychometric test that measured emotional and social impairment in order to assess participants' mental state at the time of the assessment. Since low mood and depression are known to have negative consequences on cognitive test performance (Strauss et al., 2006), it was important for the researcher to

eliminate depression as a plausible rival hypothesis for any low performances in the cognitive tests.

2.7 Neuropsychological Testing

Because internal cognitive processes do not allow for direct observation, cognitive abilities must be inferred from overt behaviour (Lezak et al., 2012). This inference is made possible by neuropsychological tests, which measure cognitive functions on a standardised scale (Lezak et al., 2012). The key to fair and unbiased neuropsychological testing is to select tests that are most appropriate for the population group and to compare subjects' performance to an appropriate reference group or norm (Skuy, Schutte, Fridjhon & O'Carroll, 2001). The neuropsychological tests selected for this study are discussed in great detail in the next chapter. There it will be seen that a single test permits assessment of a variety of cognitive functions, as the functional tasks activate a number of different regions in the brain (Anderson et al., 2008; Strauss et al., 2006).

The reason why a single neuropsychological test can provide a rich source of information about cognitive functioning is linked to the vast amount of integration that occurs in the brain. Integration is the reason why very few tasks can be localised to one area in the brain, and only a few tasks can be classified as purely verbal or visuospatial in nature (Anderson et al., 2008; Lezak et al., 2012). In general, a task may be predominantly verbal in nature but is likely to contain elements of visuospatial processing, as when an individual learns a list of words by forming a pictorial representation of the words in his/her mind. Similarly, a task may be

predominantly visuospatial in nature but can contain elements of verbal processing, as when an individual draws a complex geometric figure by verbalising the components to be drawn. This again draws attention to the fact that the two cerebral hemispheres work together to carry out most complex cognitive tasks (Lezak et al., 2012).

PART III: Cranial Irradiation, its Treatment Efficacy and Long-term Toxicity

2.8 The Introduction of Cranial Irradiation

Cranial irradiation was introduced into the treatment protocols of the 1960s in response to the failure of systemic chemotherapy to cross the blood-brain barrier and penetrate the CNS (Giordano et al., 2012). This was seen in the high rate of CNS relapse at the time (ENCCA, 2013). However, soon after the introduction of 24 Gy of cranial irradiation, the rate of CNS relapse was reduced from 64% to 4% (Roberts et al., 2013). This proved that cranial irradiation was highly effective in treating paediatric leukaemia (ENCCA, 2013).

Although the inclusion of cranial irradiation led to a dramatic increase in survivorship, it was soon discovered that it had toxic effects on brain function (Giordano et al., 2012; Keene & Oeffinger, 2001). One of the main effects that manifested some years after treatment was cognitive impairment. The IQ scores in patients irradiated with 24 Gy dropped by 10 points, and more than 50% of survivors had mild to moderate learning problems (Keene & Oeffinger, 2001). The learning difficulties reported were mostly in the areas of visuopatial processing, visuospatial memory, attention, and mathematics (Keene & Oeffinger, 2001). It is noteworthy that

visuospatial abilities have historically been affected by cranial irradiation more than verbal abilities. This is likely due to the extent of radiation-induced white matter damage in the brain, which especially impacts visuospatial functions (Anderson et al., 2008; Filley, 2005). In contrast, verbal abilities are unaffected by white matter changes (Anderson et al., 2008; Filley, 2005). In response to the finding that 24 Gy of cranial irradiation was associated with cognitive impairment, doctors were prompted to search for less toxic but still effective ways of treating leukaemia (Copeland, 1992). They began reducing the dose of cranial irradiation systematically, while trying to maintain survival rates (Keene & Oeffinger, 2001). Nowadays, prophylactic cranial irradiation is administered at doses between 12 and 18 Gy, depending on the underlying disease and risk factors (Giordano et al., 2012).

Although the reduction in dosage from 24 Gy to 18 Gy was intended to minimise the late cognitive effects, 18 Gy has still been associated with a number of cognitive deficits (Roberts et al., 2013). While the cognitive impairment at 18 Gy appears to be less profound than at 24 Gy, a degree of impairment still exists in the same cognitive domains as before (Marsh et al., 2010). However, there are marked individual differences among survivors treated with 18 Gy, with some survivors reporting a dramatic loss of cognitive function, and others reporting no problems at all (Keene & Oeffinger, 2001). This inconsistency has raised questions about the degree to which lower doses of cranial irradiation affect brain function.

A possible explanation for the inconsistencies is that the degree to which cranial irradiation affects brain function is determined by individual factors, such as the child’s age at the time of treatment, sex, and genetic inheritance (Keene & Oeffinger,

2001). Younger children are at high risk for developing cognitive deficits because cranial irradiation disrupts the rapid process of myelination in the developing brain (Anderson et al., 2008; Giordano et al., 2012). When neuronal damage is caused at an age before higher cognitive neural networks have fully developed, the resulting cognitive impairment is much more profound. This is why younger children are known to have a greater degree of cognitive impairment than older children and adults (Dockstander et al., 2013; Munch, 2013). In terms of sex, female children have been associated with more cognitive deficits than male children, although these findings are largely inconsistent (Holland, 2013). One possible explanation for the gender disparity is that the female brain undergoes more rapid neuronal development during the first few years of childhood than the male brain, possibly making the female brain more vulnerable to the effects of cranial irradiation (Copeland, 1992). These individual differences aside, any child undergoing cranial irradiation is more likely to experience long-term changes in brain function than not (Keene & Oeffinger, 2001). This is to be expected with any brain-directed therapy.

Importantly, there seems to be a dose-effect relationship observed with cranial irradiation, with larger doses associated with greater effects (Copeland, 1992). The differences in cognitive impairment between 24 Gy and 18 Gy has been well investigated, with 18 Gy typically associated with less profound cognitive impairment than 24 Gy. However, there are ongoing efforts at further dose reductions, as minimising long-term treatment toxicity remains a major goal of clinical trials. The cognitive effects emanating from 12 Gy of cranial irradiation are currently under study (Roberts et al., 2013). A recent study by Meshref, ElShazly, Nasr and AbdElhai (2013) investigated the differential effects of 12 and 18 Gy of cranial irradiation on

cognitive function in children with ALL: It was hypothesised that children irradiated with 12 Gy would exhibit less cognitive impairment than children irradiated with 18 Gy. The researchers used event related potentials to assess cognitive function. The results revealed a significantly abnormal visual component in both the 12 and 18 Gy groups; however, the 18 Gy group showed a further significantly abnormal auditory component. Slow processing speed, impaired memory and impaired attention were observed in both higher visual and higher auditory functions in the 18 Gy group, whereas only higher visual functions were affected in the 12 Gy group. Their findings also indicated a more extensive impairment of intellectual abilities in the 18 Gy group. Meshref and colleagues (2013) therefore confirmed the hypothesis that higher doses of radiation are associated with a broader spectrum cognitive impairment. Importantly, they found no significant differences in CNS relapse rate between the 12 and 18 Gy groups, advising that 12 Gy should be used in future ALL protocols.

2.9 Mechanisms of Structural Damage

Cranial irradiation directs high-energy rays to the brain in order to kill any rapidly dividing leukaemic blasts that may be present; however, it is impossible to target only cancerous cells. Although cranial irradiation has high therapeutic efficacy, one of the major disadvantages is that it also damages healthy tissue in the brain (Munch, 2013). Though the underlying mechanism for long-term cognitive impairment is not completely understood, the most widely accepted theory is that radiation induces structural white matter changes in the brain, which are followed by changes in brain function (Anderson et al., 2008; Roberts et al., 2013).

As mentioned previously, white matter tracts are bundles of myelinated axons that provide neural pathways for functional networks in the brain (McCabe & Shaw, 2010). Given the established importance of connectivity in the brain, even small white matter lesions can have a diffuse impact on cognitive function (Schuitema et al., 2013). Neuroimaging studies using magnetic resonance imaging, positron emission tomography and diffusion tensor imaging have consistently revealed significantly reduced white matter volumes in multiple brain regions in irradiated patients (Anderson et al., 2008; Copeland, 1992; Giordano et al., 2012; Hesselink, n.d.). These white matter changes seem to occur through a process of demyelination (Schuitema et al., 2013). Functionally, a reduction in white matter has been found to correlate with a reduced processing speed (Filley, 2005; Copeland, 1992; Dockstander et al., 2013; Schuitema et al., 2013). This was well established by Daams and colleagues (2012), whose magnetoencephalography recordings showed a global slowing of oscillatory brain activity after cranial irradiation. Brinkman and colleagues (2012) found that reduced white matter volumes in the brain correlated with poorer performance on tasks of executive function in survivors of childhood cancer. Anderson and colleagues (2008) explain that the extent of white matter damage is seen in low performance on visuospatial tasks and measures of sustained attention, which depend highly on integration. In contrast, patients with white matter damage are unaffected on verbal list-learning tasks because verbal memory depends more on the deep grey matter structures of the brain, such as the hippocampus (Anderson et al., 2008). Anderson and colleagues (2008) confirmed that cranial irradiation differentially affects white matter over grey matter in the brain, as participants showed significantly reduced performance on tasks reflecting white matter functioning (visuospatial and sustained attention tasks) in comparison to tasks reflecting grey matter functioning (verbal

learning and memory tasks). Filley (2005) described that patients with white matter disorders typically display deficits in sustained attention and executive functions, which are intimately associated with the integrity of the prefrontal cortex. Interestingly, Filley (2005) explained that most white matter disorders have a preference for frontal white matter, which explains why executive functions tend to become impaired after cranial irradiation. Daams and colleagues (2012) found that the white matter changes in the right frontal region seem to be primarily responsible for deficits in sustained attention. This is understood in the context of Lezak and colleagues' (2012) theoretical account of the right prefrontal cortex's involvement in sustained attention.

In looking at the pattern of white matter changes associated with cranial irradiation, there are significantly reduced white matter volumes in two out of the four major lobes of the brain, namely the frontal and parietal lobes (Brinkman et al., 2012; Giordano et al., 2012; Schuitema et al., 2013). A compelling explanation for this involves the fact that the axons in the frontal and parietal lobes myelinate at a later age than the rest of the brain (Schuitema et al., 2013). Cranial irradiation administered at a young age depletes the supply of oligodendrocytes, which are the supporting cells required for the formation of myelin sheaths in the CNS (Greene-Schloesser et al., 2012; Schuitema et al., 2013). A failure to replace oligodendrocytes interrupts the process of myelination, which may be the precise mechanism by which cranial irradiation causes damage to the developing brain (Greene-Schloesser et al., 2012). By damaging the myelin-forming cells, axons in the frontal and parietal lobes of young children may never fully myelinate, leading to challenges in further cognitive development (Holland, 2013). Brinkman et al. (2012) posit that the executive

dysfunction observed in child survivors is related to reduced white matter volumes in the fronto-parietal network, which supports the integration and control of executive functions in the brain (Brinkman et al., 2012). Silk and colleagues (2006) further note that the fronto-parietal network is responsible for attentional control in respect of visuospatial tasks. This is why, in addition to executive functions such as attention and working memory, visuospatial functions are negatively affected by cranial irradiation. However, Brinkman and colleagues (2012) note that executive functions are affected more than visuospatial functions because frontal lobe white matter is more severely affected than parietal lobe white matter. This suggests an increased sensitivity of the frontal lobes to cranial irradiation, which may be explained by the fact that the frontal lobes are the last lobes of the brain to fully develop (Samango-Sprouse, 2007).

It is important to understand that the white matter changes caused by cranial irradiation are progressive. The changes are only visible on neuroimaging scans about 6 months after cranial irradiation, and once they appear, they tend to gradually worsen over a period of 3 years (Giordano et al., 2012; Hesselink, n.d.). This physiological change has been associated with a cumulative progression of cognitive impairment, persisting for up to 10 years after treatment (Daams et al., 2012; Giordano et al., 2012). From the vantage point of a child survivor, this 10-year period of progressive cognitive decline spans most of their further academic development, which is why learning difficulties are at the forefront of issues reported by child survivors.

2.10 Long-Term Cognitive Sequelae

This section addresses the long-term cognitive sequelae of radiation-induced white matter damage in the brain. Some of the most commonly reported problems among child survivors of leukaemia involve changes in the way they think, remember and learn (Keene & Oeffinger, 2001). The cognitive impairment usually begins with deficits in processing speed, followed by attention and memory deficits, then visuospatial difficulties, and finally deficits in abstract reasoning (Holland, 2013). This cumulative progression means that children who have been off treatment for longer periods of time will show a greater level of cognitive impairment than those who have recently completed treatment (National Cancer Institute, 2014b).

Even at the relatively low doses of cranial irradiation used today, child survivors exhibit impairment in intellectual functioning, neuropsychological functioning and academic performance (Raymond-Speden et al., 2000). The most notable declines are observed in executive functions, namely attention and working memory, which are related to a reduced processing speed (Dockstander et al., 2013; National Cancer Institute, 2014b; Shuitema et al., 2013). Executive functions are most affected by cranial irradiation because treatment occurs at an age before the prefrontal cortex has fully developed. A decreased ability for attention is one of the foremost consequences of reduced white matter volumes in the prefrontal cortex (Holland, 2013). Survivors tend to have deficits in both selective and sustained attention, and also experience difficulty in switching attention from one task to another (Holland, 2013; Raymond-Speden et al., 2000). These attention deficits are more pronounced in children who are younger than 8 years old at the time of diagnosis, and in children who are treated with

higher doses of cranial irradiation (Holland, 2013). Although the attention deficits in survivors of leukaemia have a similar presentation to developmental attention deficit disorder, the nature of the problem differs fundamentally in that few survivors demonstrate significant hyperactivity or impulsivity (National Cancer Institute, 2014b). This suggests that the ventromedial prefrontal cortex, the area responsible for impulse control, is not affected by cranial irradiation. Rather, the attention deficits observed in survivors are typically associated with a slowed processing speed, which results in a global slowing of cognition (Lezak et al., 2012).

Another frequently reported issue is impaired visuospatial processing, which may be a consequence of the reduced capacity of the executive system for adequate planning and organisation (Holland, 2013; Raymond-Speden et al., 2000). Importantly, these visuospatial processing deficits occur independent of motor skills, which suggests that the underlying problem with respect to visuospatial deficits is inadequate executive functioning (Holland, 2013). While visuospatial abilities are impaired following cranial irradiation, verbal abilities seem to remain intact. In fact, language appears to be the least impaired cognitive domain after cranial irradiation (Holland, 2013). This difference is reflected in the higher verbal IQ scores and lower performance IQ scores of child survivors (Holland, 2013).

Memory impairment is another debilitating consequence of radiation injury (Holland, 2013; Raymond-Speden et al., 2000). Survivors report lower rates of both immediate and delayed recall following cranial irradiation, particularly in the visual memory domain (Keene & Oeffinger, 2001; Marsh et al., 2010). This was confirmed in the original study by Whitaker and Schutte (2012), in which it was found that participants

exhibited a decline in visuospatial learning and memory. As with attention, the memory deficits present in survivors may be related to the processing speed deficits caused by radiation-induced white matter damage (Holland, 2013). However, it is also possible that the memory impairment after cranial irradiation results from damage to the hippocampus, seeing as The St Jude Children's Hospital found that memory deficits were related to the inability to consolidate new memories (Raber, 2010). It is noteworthy that the nature of the memory impairment relates to the consolidation of new memories, rather than to a loss of previously acquired knowledge (Marsh et al., 2010). Clinical trials are currently investigating the sparing of the medial temporal lobe during cranial irradiation, in order to avoid the debilitating consequence of memory impairment (Giordano et al., 2012; Greene-Schloesser et al., 2012; Marsh et al., 2010).

The final sequela for discussion is a decline in intellectual functioning. Some studies have reported a significant decline in intellectual abilities (Raymond-Speden et al., 2000), while other studies have reported intellectual abilities comparable to the normal population (Anderson et al., 2008). One possible explanation for this inconsistency is the effect of age, as children diagnosed at a young age (<7 years) tend to have a higher frequency of intellectual dysfunction than children diagnosed at an older age (Marsh et al., 2010). This is probably due to the overall vulnerability of the young brain to cranial irradiation. Where studies have reported a decline in intellectual functioning, it tends to manifest in academic difficulties and poor scholastic achievement (Raymond-Speden et al., 2000). Holland (2013) notes that children who receive cranial irradiation are seven times more likely to require special educational assistance compared to survivors who did not receive cranial irradiation.

However, this may largely be a factor of a reduced processing speed contributing to deficits in attention more than actual intellectual impairment. Like memory impairment, intellectual impairment after cranial irradiation has been found to correlate with the dose delivered to the medial temporal lobes (Marsh et al., 2010; Raber, 2010). This demonstrates the role of long-term memory in intellectual functioning. As such, the sparing of the medial temporal lobes may help to preserve intellectual abilities as well as memory. If this can be successfully achieved, the sparing of the medial temporal lobes will be a revolutionary contribution to the field of paediatric leukaemia in terms of minimising late neurocognitive toxicity.

PART IV: Research Questions

2.11 Research Questions

Given the evidence presented on cognitive dysfunction following cranial irradiation, the following primary research questions were investigated:

- Is there evidence of neuropsychological impairment in the 12 Gy subsample, and what is the extent of the impairment?
- Is there evidence of neuropsychological impairment in the 18 Gy subsample, and what is the extent of the impairment?
- What is the neuropsychological profile of the total sample?

The question of neuropsychological impairment was addressed by analysing declines in social-emotional functioning, intellectual functioning, executive functioning, and memory and learning. Social-emotional functioning was considered first in order to

evaluate whether depression could be a confounding variable in performance on the cognitive tests. Where a decline in intellectual functioning was observed, the researcher was interested in whether the decline related to verbal or visuospatial problem solving ability. A decline in executive functioning was identified by a slowed processing speed, attention deficits, and/or impaired working memory. Where attention deficits were found, the researcher was interested in whether the deficits related to sustained attention, selective attention or divided attention. Where memory and learning deficits were found, the researcher was interested in the stage of memory processing that appeared to be affected, and whether the memory deficit related to verbal or visuospatial learning.

Since organisation and planning are two highly important aspects of cognitive test performance, two subsidiary research questions followed:

- Is there evidence of organisation and planning in the verbal learning domain?
- Is there evidence of organisation and planning in the visuospatial learning domain?

Chapter 3: Methodology

3.1 Sample

Twenty children with a history of ALL or AML and who were currently in the final phase of treatment or off treatment were invited to participate in this study. The sample was sourced from two paediatric oncology units in Johannesburg, one unit in the Charlotte Maxeke Johannesburg Academic Hospital and the other unit in the Chris

Hani Baragwanath Academic Hospital. Permission to conduct the study was obtained from the paediatric oncologists in the units (Appendices G and H), from the CEO of the Charlotte Maxeke Johannesburg Academic Hospital (Appendix I), and from the head of the Radiation Oncology department at the Charlotte Maxeke Johannesburg Academic Hospital (Appendix J). Ethical approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (Appendix K).

The sampling procedure commenced with a preliminary search in the oncology case books from 2008 to 2012, which allowed the researcher to identify all children diagnosed with ALL and AML during this period. This five-year time frame was chosen as it gave the sample a good mix of children who were still receiving treatment, children who were recently off treatment, as well as children who had been off treatment for a number of years. While searching through the oncology case books, diagnosis was obviously important, as was date of birth. Eligible children had to be between 10 and 18 years old at the time of the study in order to ensure that they were of an appropriate age to complete the psychological tests. A list of eligible children was compiled, and, with the permission of the paediatric oncologists, patient files were cross-checked for the most important criterion, whether cranial irradiation had been received as part of their treatment protocol. Eligible children had to have received cranial irradiation at least 6 months prior to the study in order to control for the late onset of cognitive impairment.

The researcher approached the parents/caregivers of the children who met all of the aforementioned inclusion criteria while they were in the paediatric oncology unit for

treatment or follow-up appointments. An information sheet (Appendix B), parental consent form (Appendix C), and participant assent form (Appendix D) were given to each parent/caregiver and eligible child, with the study explained as simply as possible. In the case where the parent/caregiver was not literate in English, a willing nurse or social worker assisted the researcher in the consent process. Children who did not have a functional use of the English language were excluded from the study at this point, as a basic level of English proficiency was required for completion of the tests. Once consent had been obtained, the parents/caregivers were requested to complete a brief biographical questionnaire (Appendix E) on behalf of their children. This questionnaire included pertinent information regarding the child's home language, educational history, developmental and medical history, as well as parental education levels and household particulars, which were used to gauge socioeconomic status. Once again, assistance was provided by a nurse or social worker if the parent/caregiver was not literate in English. Based on the information provided in the questionnaire, children were excluded if they if they were not in a formal schooling system, as a level of educational attainment was required by the cognitive tasks (Shuttleworth-Edwards, van der Merwe, van Tonder & Radloff, 2013). Children were also excluded if they had previously been diagnosed with a CNS associated injury or illness that was unrelated to the treatment of leukaemia. Children who met all of the inclusion criteria were scheduled to have the assessment on the day of their next hospital appointment.

In the days leading up to the assessment, pertinent treatment history about each participant was extracted from patient files with the consent of the paediatric oncologists and the parents/caregivers. This included the dose of cranial irradiation

received (12 or 18 Gy) and when it was received, current medication, and useful information from medical consultations (which included notes on neurological integrity and comments on current school performance) (Appendix F). In order to gain further insight into current academic performance, participants were requested to bring their last school report to the assessment.

The sample that was sourced from the two paediatric oncology units in Johannesburg formed the "treatment group" in the study, which was split according to radiation dosage. In order to answer questions of comparison, the researcher made use of a suitable norm sample taken from the locally developed intelligence test, the Individual Scales for African Language Speaking Children. For the remaining tests in the battery, the researcher made use of a suitable comparison group, which comprised unpublished raw data taken from Schutte's (2012) study. A norm sample could be used for the intelligence test because it is a locally developed test, and the demographic characteristics of the norm sample were therefore comparable to those of the treatment group. Specifically, participants were comparable on factors of race/ethnicity (black/African), home language (Zulu, Sotho, Xhosa, Tswana), and socioeconomic status (low). Furthermore, the norms have been corrected for the effect of age, with norms available in 6-month intervals for ages 9 up to 19 years old (Landman, 1997). A comparison group had to be used for the remaining tests in the battery, since locally developed neuropsychological tests do not exist in South Africa. The comparison group was comparable to the sample in the present study on factors of age, race, quality of education, and socioeconomic status. The demographic characteristics of the sample in the present study and the sample in Schutte's (2012)

unpublished study are clearly outlined in Table 2 in the next chapter, and further information is provided as to the comparability of these two samples.

3.2 Instruments

The research protocol comprised six subtests from the Individual Scales for African Language Speaking Children, two subtests from the Wechsler Intelligence Scale for Children – Revised, one psychosocial inventory, and four tests of executive function and memory. Measures of visuospatial ability, processing speed, and sustained attention typically reflect white matter functioning; whereas measures of verbal ability and verbal memory typically reflect grey matter functioning (Anderson et al., 2008).

3.2.1 Individual Scales for African Language Speaking Children (IS-A)

The IS-A is a locally developed substitute for the Wechsler Intelligence Scale for Children (Landman, 1997). It consists of ten subtests designed to measure developmental intelligence in black South African learners aged 9 to 19 years old (Landman, 1997). Five language versions of the test exist, namely Xhosa, Zulu, Northern Sotho, Southern Sotho, and Tswana (Landman, 1997). The IS-A was selected as the appropriate intelligence test for this study in anticipation of the high number of black African participants in the sample. Given that quality of education plays a vital role in intelligence test performance, the researcher was prompted to select an intelligence test that was appropriate for use on local township learners (Shuttleworth-Edwards et al., 2013). Moreover, given that participants in the present study had, at some point, a high rate of absenteeism from school, it would have been

unreasonable to assess their intellectual ability using the more stringent Wechsler Intelligence Scale for Children (Shuttleworth-Edwards et al., 2013).

Although the full IS-A comprises ten subtests (five verbal and five visuospatial), a highly correlated, abbreviated version of the scale exists, which is derived from four subtests (two verbal and two visuospatial) (Landman, 1997). The abbreviated scale allows the examiner to obtain a valid estimate of the testee's general intelligence, while reducing administration time (Landman, 1997). The researcher chose to use the abbreviated scale because it was important to keep testing time to a minimum. This is because children on treatment fatigue easily and it would have been unethical to assess them for prolonged periods of time. By using the abbreviated scale, the researcher was able to administer the intelligence test in 45 minutes instead of the usual 90 minutes required by the full scale (Landman, 1997). Although the abbreviated scale has restricted implications for use, the researcher was interested in the performance profile provided by the subtests, rather than actual IQ score itself. This is because the IQ score tends to mask selective deficits in cognitive functions, as discussed previously. The four subtests from which the abbreviated scale is derived are discussed below:

3.2.1.1 Comprehension

This is a verbal subtest, containing 27 problem questions about standard social situations and everyday practices (Landman, 1997). It assesses social and logical reasoning, long-term memory, orientation towards reality, and general knowledge (Cockcroft, 2013).

3.2.1.2 Problems

This timed verbal subtest contains 25 arithmetical problems, some of which are presented orally, and others are also printed on cards for the testee to follow while the examiner presents the problems orally (Landman, 1997). The testee is required to hold the arithmetical question in mind while working out the answer. It assesses numerical and logical reasoning, working memory, and sustained attention (Cockcroft, 2013).

3.2.1.3 Block Design

This timed visuospatial subtest contains 16 cards with printed geometric designs (Landman, 1997). The testee is required to reconstruct the printed designs using between four and nine plastic blocks. This subtest evaluates visuospatial problem solving, visuospatial analysis and construction, visual perception and organisation, planning, logical reasoning, visuomotor coordination, and sustained attention (Cockcroft, 2013).

3.2.1.4 Absurdities

This is a timed visuospatial subtest, containing 18 black-and-white pictures, requiring the testee to point out what is funny or wrong in each picture (Landman, 1997). It measures basic concept formation, orientation towards reality, ability to discriminate between essential and nonessential visual information, visual perception, long-term visual memory, and the ability to understand the gestalt (Cockcroft, 2013).

The average reliability coefficients for the abbreviated scale range between .892 and .934 for the different language versions of the test (Landman, 1997). These compare

well with the reliability coefficients of the full scale, which range between .945 and .958 (Landman, 1997). In terms of validity, the Pearson correlations between the abbreviated scale and the full scale are high (between .920 and .930), indicating that the abbreviated scale is an adequate substitute for the full scale (Landman, 1997).

The researcher supplemented two further subtests from the IS-A in order to obtain an indication of verbal and visuospatial abstract reasoning. These supplementary subtests are described below:

3.2.1.5 Similarities

This subtest contains 16 verbal items, each with a pair of concepts. The testee is required to determine the degree of similarity between each item in the pair. It measures quality of verbal reasoning, verbal concept formation, long-term memory, ability to form associations, ability to classify concepts, and deduction of rules (Cockcroft, 2013).

3.2.1.6 Pattern Completion

This timed visuospatial subtest contains 24 incomplete patterns. Only three segments of the pattern are complete, leaving the testee to deduce the rule to complete the fourth segment. It measures visuospatial logical reasoning, visual perception, visual concept formation, and sustained attention (Cockcroft, 2013).

3.2.2 Wechsler Intelligence Scale for Children – Revised (WISC-R)

Like the IS-A, the WISC-R was designed to assess intelligence in children but it is more appropriate for use on well-educated, western populations (Shuttleworth-

Edwards et al., 2013). It does, however, contain two useful subtests, which are not included in the IS-A because they are believed to make a very small contribution to general intelligence (Cockcroft, 2013). They do, however, provide useful information about executive functioning, and were therefore included in the research protocol.

3.2.2.1 Digit Span

This verbal subtest measures sustained attention in terms of immediate verbal recall span (Lezak et al., 2012). It is a subspan task, in which an increasingly longer series of digits is read aloud by the examiner and the testee is required to repeat the series in the same sequence for the forward condition and in the reverse sequence for the backward condition (Strauss et al., 2006). The amount of information correctly repeated indicates the size of the testee's attentional capacity (Lezak et al., 2012). Digits Forward taps auditory attention and short-term auditory memory, while Digits Backward taps working memory as it measures the testee's ability to manipulate information while in temporary storage (Lezak et al., 2012). The backward condition is more complex that the forward condition because it involves mental double-tracking, such that both auditory memory and reverse sequencing must proceed at the same time (Lezak et al., 2012).

The test-retest reliability coefficients for the Digit Span subtest range from .66 to .89, suggesting adequate to high reliability (Lezak et al., 2012).

3.2.2.2 Coding

This timed visuospatial subtest is a test of psychomotor speed (Lezak et al., 2012). A key is provided at the top of the page with digits from one to nine, each paired with a

nonsense symbol. The testee is required to transcribe the symbols for a random presentation of 93 digits in a 120 second period (Cockcroft, 2013). This subtest also measures visual scanning, visual-associative learning, visuomotor coordination, and sustained attention (Cockcroft, 2013; Lezak et al., 2012).

The test-retest reliability for the Coding subtest is high, with reliability coefficients in the range of .83 to .86 (Lezak et al., 2012).

3.2.3 Rey-Osterrieth Complex Figure Test (ROCFT)

The ROCFT assesses visuospatial constructional ability and long-term visual memory in individuals aged 6 to 93 years (Strauss et al., 2006). The testee is presented with a geometric figure constructed using angles and lines, and is required to copy the figure using only a pencil and a free hand. The copy trial provides an indication of visual constructional ability (Strauss et al., 2006). Demands on executive functioning are particularly high in this trial, as copying the figure requires effective organisation and planning (Lezak et al., 2012). The ROCFT was therefore also considered to be an important test of executive functioning in this study. The copy trial is followed by a delayed-recall trial administered 30 minutes later, in which the testee is required to redraw the figure from memory. The delayed-recall trial measures long-term visual memory (Strauss et al., 2006).

The ROCFT has high construct validity as it measures both copy and delayed-recall, which have strong visuospatial and visual memory components (Lezak et al., 2012). In children, scores on the ROCFT are moderately correlated with performance on other visuospatial tests, such as Block Design (Strauss et al., 2006). The ROCFT has

good internal consistency reliability with split-half and alpha coefficients greater than .60 for the copy trial and .80 for the delayed-recall trial (Lezak et al., 2012). High test-retest reliability is noted with a correlation coefficient of .89 for delayed-recall (Lezak et al., 2012). Test-retest reliability using alternate forms range from .60 to .76 (Lezak et al., 2012). Interscorer reliability is also high, with r = .91-.98.

Strauss and colleagues (2006) emphasise the importance of considering the executive aspects of ROCFT performance when interpreting the actual score. This is because both copy and delayed-recall accuracy scores tend to correlate with the organisational approach employed in constructing the figure (Strauss et al., 2006). The colour pencil method was used in order to assess participants' method of construction, which involved changing the colour pencil as an identifiable section of the figure was completed (Lezak et al., 2012). By observing the order of colour pencils used, the participant's drawing was analysed for one of three strategies:

- Piecemeal (lacking in structure such that individual details can be recognised but not the figure as a whole);
- Analytic (each element is drawn one next to the other, from left to right, generating a recognisable figure);
- Gestalt (the outline of the whole figure is drawn with all the interior details then placed inside).

The gestalt strategy, which is mediated by the right parietal lobe, reflects the highest level of organisation in the visuospatial domain (Devinsky & D'Esposito, 2004; Strauss et al., 2006). Lesions in the right parietal lobe tend to result in the production of a spatially disorganised copy, yet one that is preserved in detail (Devinsky & D'Esposito, 2004). The analytic approach, which is mediated by the left parietal lobe,

is a more detail-orientated approach in comparison to the gestalt approach (Devinsky & D'Esposito, 2004; Strauss et al., 2006). Lesions in the left parietal lobe tend to result in the construction of a figure with a general outline, yet one that is lacking in internal detail (Devinsky & D'Esposito, 2004).

3.2.4 Rey-Auditory Verbal Learning Test (RAVLT)

The RAVLT is a supraspan list-learning test commonly used to assess verbal learning and memory in individuals aged 6 to 89 years (Strauss et al., 2006). It consists of five learning trials to assess immediate verbal memory span (Trial 1) and learning rate (Trials 1-5), a sixth trial to assess susceptibility to proactive interference, a seventh trial to assess retention and susceptibility to retroactive interference, an eighth trial to assess long-term verbal memory and forgetting, and finally, a recognition task (Strauss et al., 2006). During the first five learning trials, the examiner reads out a list of words (List A) containing 15 nouns presented in a fixed order. The testee is required to recall as many List A words as possible for each of the five trials. Auditory attention is particularly important in the learning trials (Lezak et al., 2012). In the sixth trial, a distractor list of 15 nouns (List B) is read out to the testee, who is required to recall only List B words. At this point, the examiner is able to assess the effect of proactive interference from List A words. In the seventh trial, the testee is required to recall only List A words, this time without the presentation of List A by the examiner. This allows for the assessment of short-delay recall and retroactive interference from List B words. A 30-minute delay is given before the eighth trial is administered, which assesses long-term recall of List A words. The delayed-recall trial indicates the number of words retained by the testee over time. Finally, the recognition task involves reading out a combination of List A and List B words, as

well as other nouns, and the testee is required to correctly identify List A words only. This allows the examiner to assess sustained attention and separate out factors of free-recall and recognition memory.

The RAVLT has high construct validity as it measures multiple aspects of verbal memory including immediate-recall, delayed-recall, susceptibility to interference, and recognition (Lezak et al., 2012). Factor analytic studies have shown that the learning measures of the RAVLT (Trial 5, Trial 6, and the recognition task) correlate moderately well with other learning measures, with correlation coefficients ranging from .50 to .65 (Lezak et al., 2012). The Total Learning score has high internal reliability with coefficient alpha of .90 (Strauss et al., 2006). It has high test-retest reliability using alternate forms and a retest interval of one month, with correlations ranging from .61 to .86 for Trials 1-5, and from .51 to .72 for delayed-recall and recognition (Lezak et al., 2012). Test-retest reliability correlation coefficients after one year range from .38 (Trial 6) to .70 (Trial 5), suggesting adequate test-retest reliability (Lezak et al., 2012).

Strauss and colleagues (2006) explain that strong performance on the RAVLT requires effortful encoding strategies in working memory. Therefore, the order of word recall was noted in order to assess the executive aspects of RAVLT performance. Order of word recall was analysed for one of three strategies:

- Rote or haphazard recall (lacking in strategy);
- Phonetic clustering (words grouped together based on sound);
- Semantic clustering (words grouped together based on meaning).

While a semantic clustering approach is considered to be the highest organisational approach in the verbal domain, Strauss and colleagues (2006) admit that the RAVLT words do not show a clear semantic relationship. They suggest that temporal tagging may be a more important approach in the RAVLT, which is why participants' recall was also analysed for serial position effects. Recency effects are observed when words at the end of the list are recalled first, and primacy effects are observed when words at the beginning of the list are recalled first (Greene, Prepscius & Levy, 2000). Greene and colleagues (2000) explain that short-term memory is involved in the recency effect because it is responsible for maintaining the last few words in the list. As such, it was expected that the recency effect would predominate in the learning trials of the RAVLT, which assess immediate verbal memory span. The primacy effect, on the other hand, is associated with long-term memory because words at the beginning of the list have a greater chance of being consolidated in long-term memory (Greene et al., 2000). A strong primacy effect was therefore expected in the delayed-recall trial of the RAVLT, which assesses long-term verbal memory.

3.2.5 Trail Making Test (TMT)

The TMT provides a measure of attention, processing speed and working memory in individuals aged 9 to 89 years (Strauss et al., 2006). It is commonly used to assess executive functioning, and has proven to be a general and consistent indicator of neurological integrity (Strauss et al., 2006). In particular, it assesses complex visual scanning and visuomotor tracking, divided attention, and working memory (Lezak et al., 2012). The TMT consists of two parts, namely TMT-A and TMT-B. TMT-A is a relatively simple task and requires the testee to connect 25 encircled numbers in the correct chronological order. It is primarily a test of sustained attention. TMT-B is a

more complex task because it requires the testee to connect numbers in chronological order and letters in alphabetical order, but in an alternating sequence of 1-A, 2-B, 3-C, etc. The task of alternate sequencing requires mental double-tracking, working memory, and divided attention (Strauss et al., 2006). This makes TMT-B a good test of executive function. TMT-B also makes greater demands on visual search and motor speed than TMT-A, such that a low score on TMT-B relative to TMT-A may reflect the increased demands on cognitive resources in TMT-B (Strauss et al., 2006). Individuals who complete TMT-A in a much shorter time than TMT-B may have difficulties with mental double-tracking and working memory (Lezak et al., 2012). Evidence suggests that TMT-B requires the intact functioning of the dorsolateral prefrontal cortex, an area associated with functional working memory (Lezak et al., 2012). In both TMT-A and TMT-B, the numbers (and letters) are arranged in a random order on the page, requiring the testee's visual search and visual scanning abilities to be intact.

Reliability coefficients vary and are often lower for TMT-A and higher for TMT-B (Lezak et al., 2012). Test-retest reliability in adolescents is low for TMT-A (r = .41) and moderate for TMT-B (r =.65) (Strauss et al., 2006). TMT-A and TMT-B correlate moderately well with each other (r = .31-.60), suggesting that they measure similar although somewhat different functions (Strauss et al., 2006). The speed on TMT-A correlates moderately well with other timed visual search tests, such as Coding (Lezak et al., 2012). The speed on TMT-B has been correlated with Digits Backward, with a correlation coefficient of .54 (Lezak et al., 2012). This correlation points to the working memory component in of each of these tests.

3.2.6 Delis-Kaplan Executive Functioning System (D-KEFS) Colour-Word Interference Test (CWIT)

The D-KEFS is a psychological test battery designed to measure executive functioning in individuals aged 8 to 89 years (Strauss et al., 2006). The CWIT is a subtest in the D-KEFS that measures selective attention and inhibition as component processes of executive functioning (Lezak et al, 2012). It is more challenging than the traditional Stroop test because it includes an additional higher-level condition, which assesses inhibition of an overlearned response *as well as* cognitive flexibility (Strauss et al., 2006). The first two conditions in the CWIT are baseline conditions, with the first condition (Colour Naming) requiring the testee to name colour patches, and the second condition (Word Reading) requiring the testee to read colour words printed in black ink. The last two conditions are higher-level conditions, with the third condition (Interference) requiring the testee to name the dissonant ink colour in which the colour words are printed, and the fourth condition (Interference/Switching) requiring the testee to switch between naming the dissonant ink colours and reading the words that are enclosed in rectangles. Generally, it takes longer to name the colour patches than it does to read the words, and even longer to name the ink colour in which conflicting words are printed (Lezak et al., 2012). The decrease in colour naming speed is known as the "colour-word interference effect" (Strauss et al., 2006). Individuals who are particularly slow in the interference condition typically have difficulties with selective attention, as they struggle to sustain attention in the presence of distractors (Lezak et al., 2012). Given that the CWIT is a test of executive function, frontal lobe integrity is crucial for adequate performance. Damage to the frontal lobe is associated with an increased interference effect due to difficulties with inhibition (Strauss et al., 2006).

Moderate to high internal consistency reliability was established for the CWIT, with correlation coefficients ranging between .62 to .86. The interference condition loads on a processing speed factor and therefore correlates well with Coding and TMT-A (Strauss et al., 2006). Good test-retest reliability was established for each of the four conditions, with *r* = .79 for Colour Naming, *r* = .77 for Word Reading, *r* = .90 for Interference, and *r* = .80 for Interference/Switching (Delis, Kaplan & Kramer, 2001).

3.2.7 Beck Youth Inventories – Second Edition (BYI-II)

The BYI-II is used to evaluate emotional and social impairment in children and adolescents aged 7 to 18 years old (Beck, Beck, Jolly & Steer, 2005). It was included in the research protocol to assess depression in the participants, as depression contributes to poor performance on cognitive tests. The BYI-II consists of five self-report inventories, which assess the testee's experience of Self-Concept, Anxiety, Depression, Anger, and Disruptive Behaviour (Beck et al., 2005). Each inventory contains 20 easily understandable statements about thoughts, feelings or behaviours associated with each of the five constructs. The testee is required to answer how frequently (always, often, sometimes or never) each statement is true for them in the present. All five inventories were used in this study, with the depression inventory being the most important with respect to the participants' performance on the cognitive tests.

The psychometric properties of the BYI-II indicate good internal consistency (r = .91-.96) and good test-retest reliability (r = .83-.93) (Beck et al., 2005).

3.3 Procedure

The research protocol was administered on the same day that the participants were in the paediatric oncology unit for maintenance treatment or follow-up appointments. The testing procedure was done in a quiet room in the unit while the participants were waiting to receive treatment or see the doctor. Testing was always done in the morning, when the participants were alert and cooperative.

Testing began with the administration of the Digit Span and Coding subtests from the WISC-R. Digit Span was administered first by administering Digits Forward followed by Digits Backward. The researcher read the number sequences out loud at a rate of one digit per second. Administration of each condition was discontinued when the participant incorrectly responded to two sequences in the same trial. Coding was administered next. The participant was given a short practice trial and then 120 seconds to copy as many codes as possible. This was followed by the abbreviated intelligence scale: Comprehension, Problems, Block Design and Absurdities were administered in that order. Following this, the supplementary subtests from the IS-A, Similarities and Pattern Completion, were administered. Once the intelligence testing was complete, the neuropsychological testing began. First, the verbal learning test, the RAVLT, was administered. Participants completed the first five learning trials (List A) followed by the interference trial (List B). The researcher read out the words at a rate of one word per second. Participant's responses were recorded in the order of words recalled so that the organisational strategy employed by the participant could be analysed. The researcher also noted any repetitions and/or intrusions of words, which provided an indication of self-monitoring. The interference trial was followed

by an immediate-recall trial of List A. A 30-minute delay was given before the delayed-recall trial of List A was administered. In this time, the copy trial of the ROCFT was completed. The researcher switched the colour pencil used by the participant to copy the figure as each identifiable section of the figure was completed. Another 30-minute delay was given before the delayed-recall trial of the ROCFT was administered. In this time, the procedure continued with the administration of the CWIT. The four conditions were administered in the order of Colour Naming, Word Reading, Interference, and Interference/Switching. Each condition began with a short practice trial before the test trial. The researcher recorded the time it took the participant to complete each condition, as well as any errors made to provide an indication of attention and self-monitoring. Following the CWIT was the TMT. TMT-A was administered first, followed by TMT-B. Each part began with a short practice trial followed by the test trial. The researcher recorded the time it took the participant to complete each part of the TMT, as well as any errors made in each part. Once again, the errors provided an indication of attention and self-monitoring. The TMT was followed by the delayed-recall and recognition trials of the RAVLT, as well as the delayed-recall trial of the ROCFT. The BYI-II was completed at the end of the procedure. Due to the effects of fatigue, the researcher administered the BYI-II verbally and recorded the participant's responses to each item. The entire assessment procedure lasted approximately 3 hours, including adequate time to rest in between tasks.

3.4 Research Design

This study was a non-IV manipulated, cross-sectional, quasi-experimental, post-test only, with a comparison group, design. No manipulations to the independent variable were made, as all the participants had already received cranial irradiation at the time of the study. The treatment group comprised participants with leukaemia, which was compared to a sample of healthy, unaffected participants i.e. the comparison group. As such, there was no random assignment in this study. The post-test design was deemed appropriate, as the purpose of this study was to evaluate neuropsychological functioning after treatment with cranial irradiation. A pre-test was deemed inappropriate for three reasons: Firstly, when children are initially diagnosed with leukaemia, they are in their most vulnerable state. It would be unethical to assess children at this vulnerable time. Secondly, given the length of treatment (1.5 to 3 years), maturation effects may confound the differences in pre-test/post-test performance, particularly when children are developing rapidly. Moreover, a longitudinal design would be required for a pre-test/post-test design, which was not permitted by the time frame allowed for the Masters study. Given the impracticalities of a pre-test, a post-test only design was deemed appropriate. Since the research design was not a true experimental design, a control group was not used. Instead, participants in this study were compared to a local norm group and also to a local comparison group, both of which closely resembled the demographic characteristics of participants in this study but who were healthy, unaffected children with no previous medical history.

Chapter 4: Results

4.1 Sample Characteristics

Table 2 below presents the demographic characteristics of the sample in the present study as well as the sample in the comparison group taken from Schutte's (2012) unpublished study.

Table 2

Demographic Characteristics of the Study Samples

	12 Gy (*n* = 7)	**18 Gy (*n* = 13)**	**Comparison (*n* = 70)**
Current age (yrs)			
M (SD)	13.6 (3.2)	14.2 (2.9)	14.4 (0.9)
Mdn	13.9	13.8	14.6
Min.	10.0	10.7	12.7
Max.	19.1	19.2	17.2
Gender			
Male	86%	46%	51%
Female	14%	54%	49%
Diagnosis			
ALL	86%	62%	
AML	14%	38%	
Age at diagnosis (yrs)	10.2 (3.2)	11.3 (3.1)	
Time since radiation (yrs)	2.6 (1.6)	2.4 (1.5)	
Race/ethnicity	Black/African (1 Coloured)	Black/African (1 Indian)	Black/African
Socioeconomic status	Low	Low	Low
Quality of education	Township	Township	Township
Home language	Zulu, Xhosa, Sotho, Venda (1 Afrikaans)	Zulu, Xhosa, Sotho, Tswana (1 Afrikaans)	Zulu, Xhosa, Sotho, Tswana

Considering the treatment group as a whole (both 12 and 18 Gy subsamples), participants in the present study were predominantly black South African children with a low socioeconomic background. This demographic is typically associated with a multitude of factors contributing to poor prognosis, such as noncompliance and drug-resistant disease; however, the children who took part in this study were all in

remission or had already completed treatment, indicating a successful treatment outcome.

In comparing the treatment subsamples, there were fewer participants in the 12 Gy subsample than in the 18 Gy subsample. The majority of the 12 Gy subsample comprised male participants; whereas the 18 Gy subsample was more evenly split gender-wise. Importantly, however, the two subsamples were similar in respect of age at diagnosis and time since radiation. This was helpful since age at radiation and time since radiation are key factors contributing to the severity of late cognitive effects (Giordano et al., 2012; Keene & Oeffinger, 2001).

Table 2 above shows close comparability between the comparison group and the treatment subsamples in respect of race/ethnicity (black/African), socioeconomic status (low), home language (African), and quality of education (township). In terms of gender distribution, the 18 Gy subsample was closely comparable to the comparison group but the distribution was skewed towards males in the 12 Gy group. A skewed gender distribution did not pose a serious threat to the results of this study because there is inconsistent evidence regarding gender differences in neuropsychological test performance between male children with leukaemia and female children with leukaemia (Holland, 2013). As far as possible, the comparison group and treatment subsamples were age-comparable. The researcher maximised efforts to include as many participants as possible in the treatment group, which evidently led to a wider age range in the treatment group.

In order to find a way around the age confound, the use of published American norms was considered as an alternative to the comparison group; however, this option was problematic for a number of reasons. Firstly, the educational and cultural differences between the American population and the South African population invalidate comparisons between these two population groups. For example, Schmidt's (1996) metanorms for the RAVLT were conducted on high-functioning individuals who were first-language English speaking, well educated, and of high average intelligence (Strauss et al., 2006). As such, Schmidt's metanorms may overestimate the expected scores for second-language South African individuals with lower educational or intellectual levels (Strauss et al., 2006). Secondly, multiple psychological tests were used in the test battery of this study, each with its own norm sample. Comparisons would therefore have been made across multiple reference groups, all with different compositions, different geographical locations, and with data collected at different times. The differing sample characteristics of each norm sample, as well as differences in test administration, would have introduced unnecessary confounding variables into this study, which would have complicated matters further. This given, it was decided that the comparison group was the most appropriate reference group against which to compare neuropsychological test performance in this study. Use of the comparison group was valid because comparisons drew from a single sample, whose cultural and educational backgrounds were in line with those of the treatment group. This allowed for direct comparisons to be made between neuropsychological test scores (Strauss et al., 2006).

4.2 Test Scores

4.2.1 IS-A

The raw scores obtained from each participant were converted to age-corrected scaled scores using the norm tables provided in the IS-A user manuals (Landman, 1997). The scaled scores for the subtests (Comprehension, Problems, Blocks Design, Absurdities, Similarities, and Pattern Completion) have a mean of 10 and a standard deviation of 3. The abbreviated IQ score has a mean of 100 and a standard deviation of 15. Converting raw scores to scaled scores therefore allowed the researcher to compare the performance of the treatment group to a "gold standard" of 10 for the intelligence subtests and 100 for the IQ score.

4.2.2 Digit Span

The raw scores on the Digit Span test were reported in terms of a Digits Forward score, a Digits Backward score, and a Digits Total score. The reason for reporting separate scores for the forward and backward conditions is due to the misleading nature of the Digits Total score, which combines the different cognitive processes required by each part of the test into a single mental ability (Lezak et al., 2012). Due to the different cognitive demands of each part of the test, Lezak and colleagues (2012) suggest interpreting the scores for each condition separately rather than assigning meaning to the total score. A low Digits Forward score typically reflects deficits in sustained attention and self-monitoring, while a low Digits Backward score reflects working memory deficits.

4.2.3 Coding

The raw scores on the Coding subtest of the WISC-R reflect the number of blank squares correctly filled in during the 120-second time limit.

4.2.4 ROCFT

The copy and delayed-recall trials of the ROCFT were both scored using the 36-point scoring system described by Lezak and colleagues (2012). This scoring system breaks up the figure into 18 scorable elements. Each element is considered separately and assigned a score of 0, ½, 1 or 2. An element that is proportional and correctly placed is given 2 points, making the maximum score obtainable 36. A score of 1 is given if the element is distorted but correctly placed. A score of ½ is given if the element is both distorted and incorrectly placed. A score of 0 is given if the element is absent or unrecognisable. The copy score out of 36 reflects the accuracy of the original copy, and the delayed-recall score out of 36 reflects the amount of information retained over time (Strauss et al., 2006). As discussed previously, the copied figure was also described qualitatively (piecemeal, analytic, gestalt) to indicate the organisational approach used by the participant in constructing the figure.

4.2.5 RAVLT

The scores on the first five learning trials of the RAVLT reflect the number of words, out of 15, correctly recalled on each trial. The number of words recalled on Trial 1 provides an indication of immediate verbal memory span (Strauss et al., 2006). The total number of words recalled over the five learning trials reflects Total Learning, which is given as a single score out of 75 (Strauss et al., 2006). A score for Learning Over Trials was then calculated by correcting the Total Learning score for immediate

word span, using the calculation Total Learning over five trials – (5 x Trial 1 score) (Strauss et al., 2006). The score out of 15 on Trial 6 reflects susceptibility to proactive interference, and the score out of 15 on Trial 7 reflects susceptibility to retroactive interference (Blumenau & Broom, 2011). The score out of 15 on Trial 8 reflects the number of words retained by the participant over a 30-minute period. The recognition task was scored out of 15 and reflects the number of correctly identified List A words. Similar to the ROCFT, performance on the RAVLT was also described qualitatively (rote/haphazard, phonetic, semantic) to indicate the order of word recall in the learning trials and also in the delayed-recall trial.

4.2.6 TMT

Two separate scores were provided, one for TMT-A and the other for TMT-B. The scores reflect the total length of time (in seconds) it took the participants to complete each part of the test. Error scores were also provided for the TMT, as it is such a powerful indicator of neurological integrity (Strauss et al., 2006). The error scores reflect the total number of errors made on each part of the test.

4.2.7 CWIT

The four different conditions of the CWIT, Colour Naming, Word Reading, Interference, and Interference/Switching, were scored separately. Each of the four scores reflects the total length of time (in seconds) it took the participants to complete each condition of the test.

4.2.8 BYI-II

Separate scores are provided for the five different inventories in the BYI-II. Each item in each inventory was given a score of 3, 2, 1 or 0, depending on the participant's response. A score of 3 was given for 'always', 2 for 'often', 1 for 'sometimes', and 0 for 'never'. Since each inventory contained 20 items, the scores in each inventory were totaled, so that a set of five raw scores was obtained for each participant. With regard to the Self-Concept inventory, a high score reflects a good self-concept and is therefore a positive result, whereas a low score reflects a poor self-concept and is therefore a negative result. For the remaining four inventories (Anxiety, Depression, Anger and Disruptive Behaviour), a high score reflects high levels of these constructs and is therefore a negative result, whereas a low score reflects low levels of these constructs and is therefore a positive result.

4.3 Primary Data Analysis

The data obtained from the psychological tests was in the form of interval scale test scores, which allowed for quantitative statistical analyses. Age was deemed a more appropriate basis on which to compare test scores because the researcher was interested in whether the performance of the treatment group was developmentally appropriate. Although Shuttleworth et al. (2013) emphasise the value of education-based comparisons; participants in the treatment group had different educational experiences from their healthy peers due to being on treatment. In the treatment group, 14 out of 20 participants had repeated a grade. In 11 out of 14 cases, the grade that was to be repeated coincided with the first year on treatment, a time of frequent hospitalisation and absenteeism from school. Interestingly, the 12 and 18 Gy

subsamples showed similar repeat rates, suggesting that the reason for repeating a grade was primarily due to the high rate of absenteeism during the first year of treatment rather than to differences in cognitive abilities between the groups as such.

The three primary research questions outlined in chapter 2 were answered using analyses generated in SPSS (version 22). The first analysis was conducted to determine whether there was evidence of neuropsychological impairment in the 12 Gy subsample, and the second analysis was conducted to determine whether there was evidence of neuropsychological impairment in the 18 Gy subsample. These two analyses allowed the researcher to determine whether a dose-effect relationship exists in respect of cognitive impairment after treatment with cranial irradiation. The third analysis was conducted to determine the performance profile of the total sample, and was an important analysis because the larger size of the total sample provided more powerful statistical results than the subsamples on their own. The third analysis can be viewed as a summary of neuropsychological impairment after treatment with prophylactic cranial irradiation for acute leukaemia.

The researcher used box plots to detect outliers and check for normality in the data set. There were a small number of outliers in some of the psychological test scores, which, upon further exploration, generally came from participants at the extremes of the age range. Due to the already limited sample size in this study, the researcher was reluctant to remove outliers from the data set. Moreover, the removal of outliers is based on the assumption that some kind of error has been made, and that the outlier is an incorrect value (Ghosh & Vogt, 2012). This was not the case in this study, in which the outliers were genuine (but extreme) values. An alternative technique used

to deal with outliers in this case is Winsorising, in which the extreme values are replaced with the next highest or lowest value in the data set that is not considered to be an outlier (Howell, 2008). Although Ghosh and Vogt (2012) believe that this technique may undervalue the outliers, Howell (2008) claims that Winsorising does not substantially change the distribution. Rather, it has a similar effect on the mean as if the outliers had been removed (Howell, 2008). The researcher therefore decided to employ the Winsorising technique, as it was a middle-ground approach between treating the outliers as data points and removing the outliers all together (Ghosh & Vogt, 2012).

In terms of normality, the data was not expected to approximate a normal distribution given the small number of participants in the treatment subsamples (n = 7 for 12 Gy and n = 13 for 18 Gy). The graphic representation provided by the box plots also confirmed that some of the data was sufficiently skewed. As a result, the researcher decided to run nonparametric statistical analyses on the data. One-sample Wilcoxon signed-rank tests were conducted to compare intelligence test scores in the treatment group to the norm sample from the IS-A. The researcher wanted to determine if the median of the treatment group differed significantly from the known mean of the norm sample (μ), with μ = 10 for the subtests and μ = 100 for the IQ score. An alpha level of .05 was used. Wilcoxon Mann-Whitney tests were conducted to compare neuropsychological test scores in the treatment group to the comparison group. The researcher wanted to determine if the mean ranks of the treatment group differed significantly from the mean ranks of the comparison group. An alpha level of .05 was used. Although the Wilcoxon Mann-Whitney test does not compare medians, in most

cases, the group with the higher mean rank also had the higher median. For convenience purposes, medians have been reported.

Effect sizes (*r*) were calculated using the effect size formula for Wilcoxon tests, $r = Z/\sqrt{N}$, where *Z* is the standardised test statistic (Wilcoxon's *W* converted into a z-score in SPSS) and *N* is the total sample size. Despite the presence of *N* in the formula, effect size is independent of how many people were tested (Fritz, Morris & Richler, 2012). This is because *Z* is sensitive to sample size, so dividing by a factor of *N* removes the effect of sample size from the resultant effect size (Fritz et al., 2012). In all cases, absolute values of *r* have been reported. The practical effect of a significant difference has been described as small if *r* = .1 to .3, moderate if *r* = .3 to .5, large if *r* = .5 to .8, and very large if *r* > .8 (Fritz et al., 2012).

The research questions will now be addressed individually.

Is there evidence of neuropsychological impairment in the 12 Gy subsample?

Table 3

Summary Statistics for Social-Emotional Functioning in the 12 Gy Subsample

Beck Youth Inventory	***M***	***Mdn***	***SD***
Self-Concept	46.43	44.00	4.76
Anxiety	17.57	17.00	6.65
Depression	11.86	13.00	7.63
Anger	11.57	12.00	7.02
Disruptive Behaviour	4.86	6.00	3.89

Table 4

Wilcoxon Mann-Whitney Tests for Social-Emotional Functioning in the 12 Gy Subsample

Beck Youth Inventory	*N*	*Z*	*p*	*r*
Self-Concept	78	-1.689	.092	.191
Anxiety	78	-.228	.827	.026
Depression	78	-.201	.847	.023
Anger	78	-.044	.969	.005
Disruptive Behaviour	78	-1.158	.255	.131

There were no significant signs of emotional or social impairment in the 12 Gy subsample.

Table 5

Summary Statistics for Intelligence Test Performance in the 12 Gy Subsample

IS-A Subtests	*M*	*Mdn*	*SD*
Comprehension	11.29	12.00	2.50
Problems	11.00	12.00	1.41
Block Design	12.43	12.00	1.40
Pattern Completion	10.57	10.00	1.40
Absurdities	12.29	12.00	1.89
Similarities	8.86	8.00	2.04
Abbreviated IQ	108.43	114.00	16.40

Table 6

One-Sample Wilcoxon Signed-Rank Tests for Intelligence Test Performance in the 12 Gy Subsample

IS-A Subtests	*N*	*Z*	*p*	*r*
Comprehension	7	1.207	.227	.456
Problems	7	1.734	.083	.655
Block Design	7	2.379	.017*	.899
Pattern Completion	7	1.242	.214	.469
Absurdities	7	2.032	.042*	.768
Similarities	7	-1.372	.170	.519
Abbreviated IQ	7	1.185	.236	.448

*$p < .05$

As can be seen in Table 6 above, the performance of the 12 Gy subsample on the Block Design subtest was significantly above that of the norm sample, and the practical effect was very large. Similarly, the performance of the 12 Gy subsample on the Absurdities subtest was significantly above that of the norm sample, with a large practical effect.

Table 7

Summary Statistics for Neuropsychological Test Performance in the 12 Gy Subsample

Psychological Test	***M***	***Mdn***	***SD***
WISC-R			
Digits Forward	5.71	6.00	0.49
Digits Backward	4.29	4.00	0.49
Digits Total	10.57	10.00	1.51
Coding	41.00	41.00	11.55
ROCFT			
Copy	28.29	28.00	2.86
Delayed Recall	16.93	13.00	7.81
RAVLT			
Trial 1	5.43	6.00	2.23
Trial 2	7.71	8.00	2.21
Trial 3	9.43	11.00	3.78
Trial 4	10.29	11.00	2.50
Trial 5	10.57	12.00	3.05
Trial 6 (Interference)	5.00	5.00	1.00
Trial 7 (Retention)	8.14	8.00	2.79
Trial 8 (Delayed Recall)	9.14	10.00	3.44
Total Learning	43.43	49.00	13.07
Learning Over Trials	15.00	14.00	3.16
Recognition	14.57	15.00	0.53
TMT			
Part A Time	44.50	45.50	13.49
Part A Errors	0.29	0.00	0.49
Part B Time	122.29	113.00	74.32
Part B Errors	0.43	0.00	0.53
CWIT			
Colour Naming	46.14	47.00	10.56
Word Reading	39.29	36.00	13.49
Interference	84.29	80.00	23.76
Interference/Switching	91.17	83.50	36.48

Table 8

Wilcoxon Mann-Whitney Tests for Neuropsychological Test Performance in the 12 Gy Subsample

Psychological Test	***N***	***Z***	***p***	***r***
WISC-R				
Digits Forward	77	-.155	.886	.018
Digits Backward	77	-.980	.329	.112
Digits Total	77	-1.154	.258	.132
Coding	77	-.390	.706	.044
ROCFT				
Copy	78	-.993	.330	.112
Delayed Recall	78	-.700	.495	.079
RAVLT				
Trial 1	78	-.133	.903	.015
Trial 2	78	-.664	.518	.075
Trial 3	78	-.443	.668	.050
Trial 4	78	-.240	.813	.027
Trial 5	78	-.424	.683	.048
Trial 6 (Interference)	77	-.649	.525	.074
Trial 7 (Retention)	78	-.980	.338	.111
Trial 8 (Delayed Recall)	77	-.340	.743	.039
Total Learning	78	-.245	.814	.028
Learning Over Trials	78	-.779	.446	.088
Recognition	78	-.944	.383	.107
TMT				
Part A Time	77	-.200	.849	.023
Part A Errors	78	-1.663	.149	.188
Part B Time	78	-.394	.703	.045
Part B Errors	78	-.288	.863	.033
CWIT				
Colour Naming	78	-1.514	.133	.171
Word Reading	78	-2.244	.023*	.254
Interference	78	-1.225	.228	.139
Interference/Switching	77	-.466	.653	.053

*$p < .05$

As can be seen in Table 8 above, the 12 Gy subsample was significantly slower to complete the Word Reading condition of the CWIT than the comparison group. The practical effect of this difference was small.

Is there evidence of neuropsychological impairment in the 18 Gy subsample?

Table 9

Summary Statistics for Social-Emotional Functioning in the 18 Gy Subsample

Beck Youth Inventory	***M***	***Mdn***	***SD***
Self-Concept	42.30	44.00	8.68
Anxiety	25.80	27.00	6.75
Depression	16.10	13.50	8.33
Anger	20.00	18.00	12.45
Disruptive Behaviour	8.30	6.00	7.33

Table 10

Wilcoxon Mann-Whitney Tests for Social-Emotional Functioning in the 18 Gy Subsample

Beck Youth Inventory	***N***	***Z***	***p***	***r***
Self-Concept	81	-.316	.758	.035
Anxiety	81	-2.602	.008*	.289
Depression	81	-1.473	.143	.164
Anger	81	-1.914	.055	.213
Disruptive Behaviour	81	-.050	.963	.006

*$p < .05$

As can be seen in Table 10 above, anxiety levels were significantly higher in the 18 Gy subsample than in the comparison group. The practical effect of this difference was small.

Table 11

Summary Statistics for Intelligence Test Performance in the 18 Gy Subsample

IS-A Subtests	*M*	*Mdn*	*SD*
Comprehension	9.20	10.00	3.39
Problems	8.10	8.50	2.51
Block Design	8.46	8.00	1.13
Pattern Completion	7.46	6.00	3.43
Absurdities	9.00	9.00	3.03
Similarities	8.70	8.50	2.75
Abbreviated IQ	92.10	89.00	15.31

Table 12

One-Sample Wilcoxon Signed-Rank Tests for Intelligence Test Performance in the 18 Gy Subsample

IS-A Subtests	*N*	*Z*	*p*	*r*
Comprehension	10	-.614	.539	.194
Problems	10	-2.038	.042*	.644
Block Design	13	-2.836	.005*	.787
Pattern Completion	13	-2.405	.016*	.667
Absurdities	13	-1.118	.264	.310
Similarities	10	-1.287	.198	.407
Abbreviated IQ	10	-1.376	.169	.435

*$p < .05$

As can be seen in Table 12 above, the performance of the 18 Gy subsample on the Problems subtest was significantly below that of the norm sample, and the practical effect was large. Similarly, the performance of the 18 Gy subsample on the Block Design subtest was significantly below that of the norm sample, and the practical effect was large. The performance of the 18 Gy subsample on the Pattern Completion subtest was also significantly below that of the norm sample, with a large practical effect.

Table 13

Summary Statistics for Neuropsychological Test Performance in the 18 Gy Subsample

Psychological Tests	***M***	***Mdn***	***SD***
WISC-R			
Digits Forward	5.00	5.00	1.26
Digits Backward	3.18	3.00	1.40
Digits Total	8.27	8.00	2.61
Coding	35.92	34.00	10.50
ROCFT			
Copy	25.69	27.00	5.25
Delayed Recall	13.58	14.50	5.78
RAVLT			
Trial 1	4.90	5.50	1.60
Trial 2	8.70	8.50	2.87
Trial 3	9.70	9.00	2.63
Trial 4	11.50	11.00	2.92
Trial 5	11.50	12.00	2.68
Trial 6 (Interference)	4.67	4.00	0.87
Trial 7 (Retention)	9.22	10.00	4.47
Trial 8 (Delayed Recall)	9.00	9.50	3.92
Total Learning	46.30	44.50	11.12
Learning Over Trials	21.80	21.00	5.98
Recognition	13.67	15.00	1.94
TMT			
Part A Time	58.92	54.00	19.32
Part A Errors	0.39	0.00	0.51
Part B Time	143.58	124.00	58.86
Part B Errors	2.75	2.00	2.42
CWIT			
Colour Naming	47.10	47.50	6.12
Word Reading	36.30	38.50	8.35
Interference	102.90	91.00	34.37
Interference/Switching	100.60	104.00	19.42

Table 14

Wilcoxon Mann-Whitney Tests for Neuropsychological Test Performance in the 18 Gy Subsample

Psychological Tests	***N***	***Z***	***p***	***r***
WISC-R				
Digits Forward	81	-1.486	.141	.165
Digits Backward	81	-1.489	.140	.165
Digits Total	81	-1.828	.068	.203
Coding	83	-.965	.340	.106
ROCFT				
Copy	84	-2.255	.023*	.246
Delayed Recall	84	-2.408	.015*	.263
RAVLT				
Trial 1	81	-.891	.381	.099
Trial 2	81	-.174	.866	.019
Trial 3	81	-.044	.969	.005
Trial 4	81	-.931	.359	.103
Trial 5	81	-.442	.665	.049
Trial 6 (Interference)	79	-1.325	.188	.149
Trial 7 (Retention)	80	-.092	.931	.010
Trial 8 (Delayed Recall)	80	-.051	.963	.006
Total Learning	81	-.108	.918	.012
Learning Over Trials	81	-2.272	.022*	.252
Recognition	80	-.106	.935	.012
TMT				
Part A Time	84	-2.487	.012*	.271
Part A Errors	84	-2.931	.011*	.320
Part B Time	83	-2.702	.006*	.297
Part B Errors	83	-3.546	<.001*	.389
CWIT				
Colour Naming	81	-2.910	.003*	.323
Word Reading	81	-2.887	.003*	.321
Interference	81	-2.708	.006*	.301
Interference/Switching	81	-3.023	.002*	.336

*$p < .05$

As can be seen in Table 14 above, the performance of the 18 Gy subsample on the copy trial of the ROCFT was significantly below that of the comparison group. The practical effect was small. Similarly, the performance of the 18 Gy subsample on the delayed-recall trial of the ROCFT was significantly below that of the comparison group, with a small practical effect. The score for Learning Over Trials in the RAVLT

was significantly higher in the 18 Gy subsample than in the comparison group, with a small practical effect. The 18 Gy subsample was significantly slower to complete TMT-A than the comparison group, with a small practical effect. The 18 Gy subsample also made significantly more errors in TMT-A, and the practical effect was moderate. Similarly, the 18 Gy subsample was significantly slower to complete TMT-B than the comparison group, with a small practical effect. The 18 Gy subsample also made significantly more errors in TMT-B, with a moderate practical effect. The 18 Gy subsample was significantly slower to complete the Colour Naming condition of the CWIT than the comparison group. The practical effect was moderate. Similarly, the 18 Gy subsample was significantly slower to complete the Word Reading condition of the CWIT, with a moderate practical effect. The 18 Gy subsample was significantly slower to complete the Interference condition of the CWIT than the comparison group. The practical effect was moderate. Similarly, the 18 Gy subsample was significantly slower to complete the Interference/Switching condition of the CWIT, with a moderate practical effect.

What is the neuropsychological profile of the total sample?

Table 15

Summary Statistics for Social-Emotional Functioning in the Total Sample

Beck Youth Inventory	***M***	***Mdn***	***SD***
Self-Concept	44.65	44.00	5.90
Anxiety	21.65	22.00	8.85
Depression	14.35	13.00	8.09
Anger	14.82	13.00	7.99
Disruptive Behaviour	7.77	6.00	7.50

Table 16

Wilcoxon Mann-Whitney Tests for Social-Emotional Functioning in the Total Sample

Beck Youth Inventory	***N***	***Z***	***p***	***r***
Self-Concept	88	-1.344	.181	.143
Anxiety	88	-1.487	.139	.159
Depression	88	-1.206	.231	.129
Anger	88	-1.255	.212	.134
Disruptive Behaviour	88	-.482	.634	.051

There were no significant signs of emotional or social impairment in the total sample.

Table 17

Summary Statistics for Intelligence Test Performance in the Total Sample

IS-A Subtests	***M***	***Mdn***	***SD***
Comprehension	9.77	11.00	3.56
Problems	9.06	9.00	2.75
Block Design	10.25	9.50	2.81
Pattern Completion	9.00	9.00	4.01
Absurdities	9.90	10.00	3.29
Similarities	8.76	8.00	2.41
Abbreviated IQ	98.82	101.00	17.36

Table 18

One-Sample Wilcoxon Signed-Rank Tests for Intelligence Test Performance in the Total Sample

IS-A Subtests	***N***	***Z***	***p***	***r***
Comprehension	17	.000	1.000	.000
Problems	17	-1.147	.252	.278
Block Design	20	.284	.777	.064
Pattern Completion	20	-1.164	.245	.260
Absurdities	20	-.167	.868	.037
Similarities	17	-1.957	.050	.475
Abbreviated IQ	17	-.261	.794	.063

There were no significant differences in intelligence test performance in the total sample.

Table 19

Summary Statistics for Neuropsychological Test Performance in the Total Sample

Psychological Tests	***M***	***Mdn***	***SD***
WISC-R			
Digits Forward	5.28	5.00	1.56
Digits Backward	3.61	4.00	1.09
Digits Total	8.89	9.00	2.76
Coding	37.70	37.50	10.86
ROCFT			
Copy	26.25	27.00	4.98
Delayed Recall	14.75	13.75	6.56
RAVLT			
Trial 1	5.12	6.00	1.83
Trial 2	8.29	8.00	2.59
Trial 3	9.77	9.00	2.51
Trial 4	11.00	11.00	2.74
Trial 5	11.12	12.00	2.78
Trial 6 (Interference)	4.81	4.50	1.33
Trial 7 (Retention)	8.75	9.00	3.75
Trial 8 (Delayed Recall)	9.06	10.00	3.61
Total Learning	45.12	48.00	11.65
Learning Over Trials	19.53	19.00	6.36
Recognition	14.31	15.00	0.87
TMT			
Part A Time	59.32	51.00	27.05
Part A Errors	0.35	0.00	0.49
Part B Time	137.32	118.00	66.62
Part B Errors	2.05	1.00	2.23
CWIT			
Colour Naming	47.00	47.00	8.31
Word Reading	37.53	38.00	10.48
Interference	93.47	83.00	27.03
Interference/Switching	97.06	98.00	26.31

Table 20

Wilcoxon Mann-Whitney Tests for Neuropsychological Test Performance in the Total Sample

Psychological Tests	***N***	***Z***	***p***	***r***
WISC-R				
Digits Forward	88	-.968	.337	.103
Digits Backward	88	-.816	.419	.087
Digits Total	88	-1.006	.318	.107
Coding	90	-.534	.598	.056
ROCFT				
Copy	91	-2.392	.016*	.251
Delayed Recall	91	-2.249	.024*	.236
RAVLT				
Trial 1	88	-.575	.571	.061
Trial 2	88	-.273	.789	.029
Trial 3	88	-.348	.732	.037
Trial 4	88	-.541	.594	.058
Trial 5	88	-.069	.947	.007
Trial 6 (Interference)	86	-1.246	.215	.134
Trial 7 (Retention)	87	-.680	.502	.073
Trial 8 (Delayed Recall)	87	-.167	.871	.018
Total Learning	88	-.228	.824	.024
Learning Over Trials	88	-1.466	.144	.156
Recognition	87	-.739	.455	.079
TMT				
Part A Time	90	-2.240	.024*	.236
Part A Errors	91	-2.981	.007*	.312
Part B Time	90	-2.285	.022*	.241
Part B Errors	90	-2.782	.005*	.293
CWIT				
Colour Naming	88	-3.062	.002*	.326
Word Reading	88	-3.480	<.001*	.371
Interference	88	-2.733	.006*	.291
Interference/Switching	87	-2.581	.009*	.278

*$p < .05$

As can be seen in Table 20 above, the performance of the total sample on the copy trial of the ROCFT was significantly below that of the comparison group, with a small practical effect. Similarly, the performance of the total sample on the delayed-recall trial of the ROCFT was significantly below that of the comparison group, with a small practical effect. The total sample was significantly slower to complete TMT-A than

the comparison group, with a small practical effect. The total sample also made significantly more errors in TMT-A, with a moderate practical effect. Similarly, the total sample was significantly slower to complete TMT-B than the comparison group, with a small practical effect. The total sample also made significantly more errors in TMT-B, with a small practical effect. The total sample was significantly slower to complete the Colour Naming condition of the CWIT than the comparison group. The practical effect was moderate. Similarly, the total sample was significantly slower in completing the Word Reading condition of the CWIT, with a moderate practical effect. The total sample was significantly slower to complete the Interference condition of the CWIT than the comparison group. The practical effect was small. Similarly, the total sample was significantly slower to complete the Interference/Switching condition of the CWIT, with a small practical effect.

Based on the z-scores and effect sizes in Tables 16, 18 and 20 above, the following neuropsychological profile (Figure 1) was obtained for the total sample (see Appendix A for a list of abbreviations and their meanings). Significant differences are at least two standard deviations below the mean, and can be identified from the graph as those columns falling below the red line.

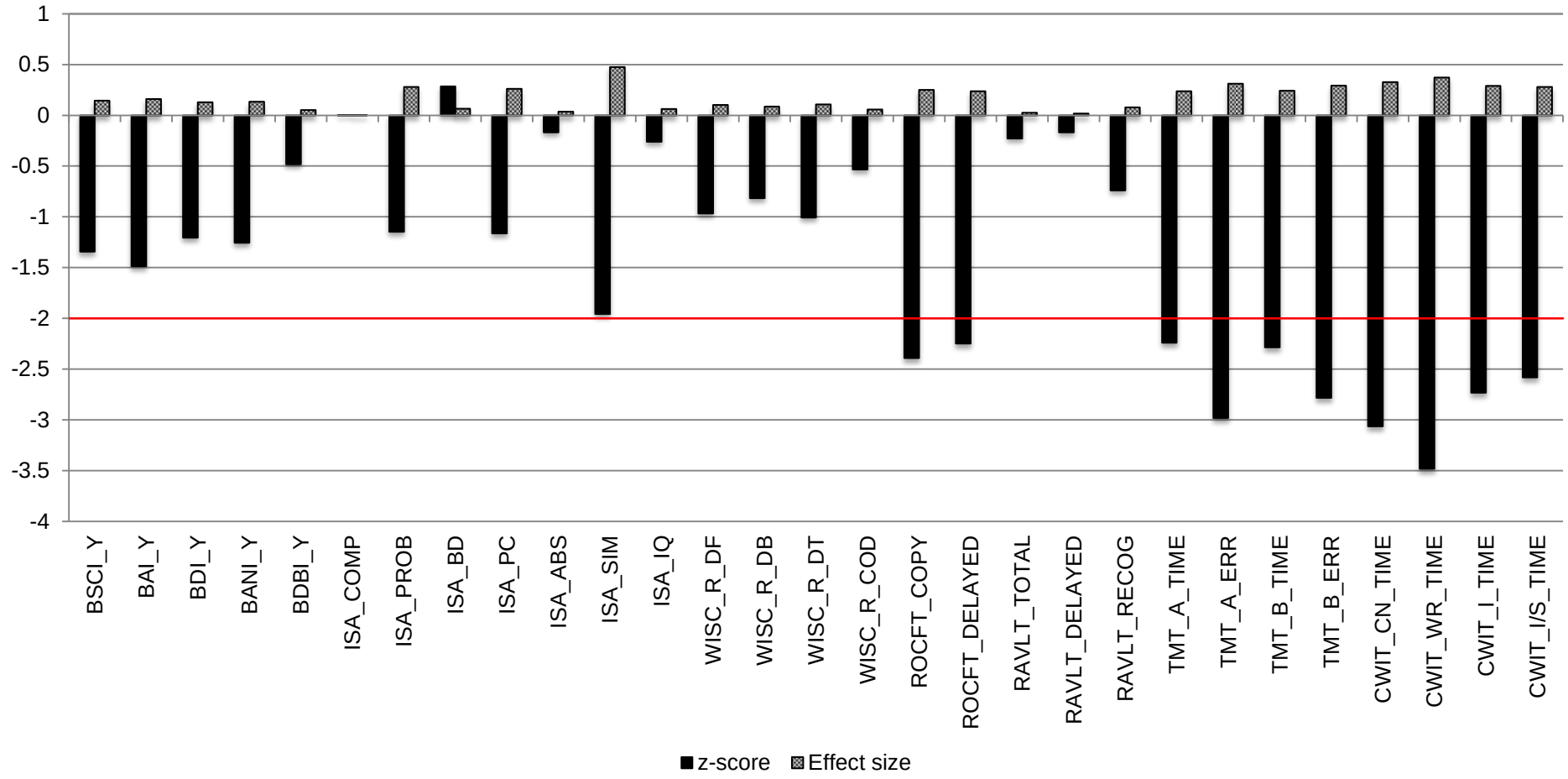


Figure 1. The neuropsychological profile of children treated with prophylactic cranial irradiation for acute leukaemia.

4.4 Subsidiary Data Analysis

The researcher was interested in the organisational strategies employed in the RAVLT and the ROCFT, the verbal and visuospatial learning tests respectively, as these strategies provide further insight into the executive functioning of the treatment group. Although these findings will not be a central topic of discussion in chapter 5, they have been included here as they may be helpful in explaining the RAVLT and ROCFT test scores in this study. The analyses below reflect the patterns observed in the total sample.

Is there evidence of planning and organisation in the verbal learning domain?

Tables 21 and 22 below show patterns of word recall and serial position effects in the RAVLT respectively.

Table 21

Organisational Approaches in the RAVLT

Strategy	Trials 1-5	Delayed Recall
Rote/haphazard	76%	65%
Phonetic clustering	0%	11%
Semantic clustering	24%	24%

Table 22

Serial Position Effects in the RAVLT

Effect	Trials 1-5	Delayed Recall
Primacy	18%	82%
Recency	82%	18%

Is there evidence of planning and organisation in the visuospatial learning domain?

Table 23 below shows the method of construction in the ROCFT.

Table 23

Organisational Approaches in the ROCFT

Strategy	Copy Trial
Piecemeal	10%
Analytic	55%
Gestalt	35%

Chapter 5: Discussion

The purpose of this discussion is to provide an integrative account of how the two subsamples fared in the major neuropsychological domains assessed in this study. It is important to discuss their performances on the various psychological tests together so that differences in cognitive functioning between the subsamples can be clearly offset. Once comparisons based on radiation dosage have been made, the performance profile of the total sample will be discussed. This is intended as a powerful summation of the findings in this study, and also to contextualise the previous study findings by Whitaker and Schutte (2012).

5.1 Social-Emotional Functioning

Before the discussion of neuropsychological impairment can begin, it is important to rule out the potential effect of depression on cognitive test performance. This was the primary reason for including the BYI-II in the research protocol.

Table 4 shows no statistically significant differences between the depression scores of the 12 Gy subsample and those of the comparison group. This means that the cognitive test performance of the two groups is comparable, and the possibility of depression accounting for any low performances in the 12 Gy subsample was eliminated.

Table 10 shows no statistically significant differences between the depression scores of the 18 Gy subsample and those of the comparison group. This eliminated the possibility of depression accounting for any low performances in the 18 Gy subsample. Table 10 does, however, show a significantly higher anxiety level in the 18 Gy subsample than in the comparison group. Although the effect size was small, this is a real effect. There are a number of possible reasons for the increased anxiety in the 18 Gy subsample. Firstly, children irradiated with 18 Gy may have a different set of risk factors from children irradiated with 12 Gy, making them generally more anxious about their disease and the treatment process. Secondly, increased anxiety has been associated with decreased activity in the anterior cingulate cortex (Ng, Chan & Schlaghecken, 2012), and cranial irradiation has been known to disrupt the fronto-parietal network, which includes the anterior cingulate cortex (Brinkman et al., 2012). As such, the anxiety present in the 18 Gy subsample may even have a physiological

basis. Although it is unclear whether the origin of the anxiety in the 18 Gy subsample is of a psychological or physiological nature, it must be acknowledged that the mildly increased level of anxiety might be partly responsible for the cognitive test performance of the 18 Gy subsample. In particular, anxiety is known to impair processing efficiency by reducing attentional control (Eysenck, Derakshan, Santos & Calvo, 2007).

In summary, the 12 Gy subsample did not show any significant signs of depression or anxiety, eliminating the possibility that low mood and affect may have impacted their cognitive test performance. While the 18 Gy subsample showed no significant signs of depression, a significantly increased level of anxiety was found, which had a small but real effect. Whether psychological or physiological in nature, the increased level of anxiety may have played a role in the cognitive performance of the 18 Gy subsample by reducing attentional focus on the current task.

5.2 Intellectual Functioning

In order to answer the question of whether there is a decline in intellectual functioning after treatment with cranial irradiation, intelligence test performance was considered. The intelligence subtests were of greater importance than the derived IQ score, as the profile of cognitive strengths and weaknesses provided more meaningful information than the IQ score on its own.

Table 6 shows significant differences in performance in both the Block Design and Absurdities subtests in the 12 Gy subsample. Although these are both visuospatial

subtests and performance was expected to be low, the performance of the 12 Gy subsample was above the norm in both cases. The large effect size for both of these subtests suggests that the advantage is evident to the naked eye. This finding is contrary to that of Meshref and colleagues (2013), who found that visuospatial abilities were impaired even at 12 Gy. It is possible that the strong performance of the 12 Gy subsample on the Block Design and Absurdities subtests in the present study was a function of increased exposure to play activities in combination with a lower dosage of cranial irradiation. In comparison to the normal population, children with leukaemia are exposed to more play and less school-related activities during treatment. While they are in hospital, children play with toys and games, and partake in various creative activities offered by CHOC volunteers, which may give them an advantage in respect of the aforementioned subtests. The Block Design subtest is the most game-like subtest in the intelligence scale, and the illustrations in the Absurdities subtest may resemble those seen in the colouring-in books or storybooks that are available in the ward. It is therefore speculated that the participants' familiarity and regular involvement in such tasks may have contributed to their superior performance. In addition to these environmental factors, 12 Gy of cranial irradiation may be a low enough dose to preserve visuospatial abilities, allowing the participants in the 12 Gy subsample to perform to the best of their ability in the visuospatial tests. In considering the derived IQ score of the 12 Gy subsample, no significant differences were found, indicating that the IQ of the 12 Gy subsample was comparable to the norm.

In the 18 Gy subsample, Table 12 shows significant differences in the Problems, Block Design and Pattern Completion subtests. In all instances, performance of the 18

Gy subsample was below the norm. The effect sizes for all of these subtests were large, suggesting that children treated with 18 Gy experience a great deal of difficulty in the cognitive domains of numerical reasoning and visuospatial problem solving. In contrast to the 12 Gy subsample, performance on the Block Design subtest was significantly lower in the 18 Gy subsample. Although participants in the 18 Gy subsample were exposed to the same hospital environment as participants in the 12 Gy subsample, the structural effects emanating from the higher dose of cranial irradiation may result in visuospatial deficits at 18 Gy, making it more difficult for participants in the 18 Gy subsample to perform well on tasks involving visuospatial problem solving, such as Block Design and Pattern Completion. Since visuospatial subtests like Block Design reflect white matter functioning and rely on the right hemisphere (Anderson et al., 2008), it is possible that right hemispheric white matter abnormalities exist at 18 Gy of cranial irradiation. Significantly lower performance on the Pattern Completion subtest confirms that visuospatial problem solving abilities are negatively affected by higher doses of cranial irradiation, and also indicates problems with visual abstract reasoning, which Anderson and colleagues (2008) identified as one of the last cognitive sequelae to develop. In contrast, verbal problem solving abilities seem to remain intact, as evident by the verbal subtest scores that fall in the average range in the 18 Gy subsample. This is in line with Holland's (2013) finding that language seems to be the least impaired cognitive domain after cranial irradiation. Significantly lower performance on the Problems subtest suggests that numerical reasoning is a problematic domain after 18 Gy of cranial irradiation. This finding supports the claim by Keene and Oeffinger (2001) that mathematics is an area of weakness in children irradiated with higher doses of radiation. What is particularly interesting is that Problems, Block Design and Pattern completion represent three out

of the four timed subtests that were selected from the IS-A for this study. This given, low performance in all three of these subtests may well reflect an underlying slowed processing speed, pointing to deficits in executive function. In other words, it is possible that the perceived intellectual impairment in the 18 Gy subsample may be more a matter of reduced white matter volumes contributing to an overall slowed processing speed, which is particularly evident in these timed cognitive tasks. In considering the derived IQ score of the 18 Gy subsample, no significant differences were found. This is likely due to the inclusion of the verbal subtests in the calculation, which may have masked the lower performances in the Block Design and Pattern Completion subtests. The misleading nature of the IQ score is exactly why it is important to consider the performance profile provided by the individual subtests rather than the IQ score itself. These findings are in line with those of Anderson and colleagues (2008), who found an average overall intelligence even in the presence of domain-specific intellectual impairment.

Lezak and colleagues (2012) note that the abilities assessed by the intelligence subtests are closely related to academic abilities. The academic difficulties encountered by child survivors tend to relate to reading and mathematics (National Cancer Institute, 2014b). The researcher was therefore interested in gathering further evidence about participants' academic performance, which was in the form of their most recent school reports. For one of the participants, the two lowest marks in the school report were mathematics (26%) and geography (17%). Interestingly, mathematics and geography are subjects that require numerical reasoning and visuospatial skills respectively, which are among the problematic domains identified in the 18 Gy subsample. This particular participant was treated with 18 Gy. A second

participant, who was also irradiated with 18 Gy, achieved 25% for mathematics in the context of a 56% grade average. One of the younger participants had recently moved to a special needs school due to problems with reading. The comment on this participant's school report was "Has shown some improvement in reading but needs to practice number patterns". This participant was irradiated with 18 Gy. The mathematics marks of some of the other participants irradiated with 18 Gy were 33%, 44% and 51%. Teachers' comments included "Work much harder at Maths" and "Needs additional support for Maths Literacy". For participants irradiated with 12 Gy, mathematics marks were 30%, 46%, 60% and 78%. The participant who received 78% was a strong learner, with all other marks well above the grade average. The participant who received 30% was advised by the teacher to move to a special needs school in the following year due to slowness in class. The majority of these cases highlight the large practical effects found in the intelligence subtests, particularly the Problems subtest. Although it is difficult to determine whether it is absenteeism from school during treatment or the treatment itself that is responsible for these academic difficulties, the teachers' comments all point to the need for remediation after treatment.

In summary, the 12 Gy subsample did not show evidence of intellectual impairment after cranial irradiation. On the contrary, their performance was significantly above the norm in two out of six intelligence subtests, which may be a combination of environmental factors and a lower radiation dosage contributing to their superior performance. However, the 18 Gy subsample showed domain-specific deficits in numerical reasoning and visuospatial problem solving. These deficits have large implications in reality, as reflected in participants' school reports. It is important to

consider, however, that the deficits in the intelligence subtests may be the manifestation of an underlying deficit in processing speed, as the deficits were found in the majority of the timed tasks. Overall intelligence was found to be intact despite the existence of domain-specific deficits. This was likely a function of the verbal subtests masking the effect of the visuospatial subtests, as verbal problem solving abilities were intact even at 18 Gy of cranial irradiation.

5.3 Executive Functions

In order to answer the question of whether executive functioning is impaired following cranial irradiation, the researcher evaluated participants' performance on tests of attention and working memory, as well as tests requiring speeded performance.

5.3.1. Attention

Attention was required in the Problems, Block Design and Pattern Completion subtests of the IS-A, Digits Forward, Coding, the learning trials and recognition task of the RAVLT, TMT-A and TMT-B, and all four conditions of the CWIT. Each of these tasks required the basic functional form of attention, sustained attention, in order to maintain concentration for the duration of the task. Over and above this, some of the more challenging tasks required a higher form of attention, such as selective or divided attention. For example, TMT-B required divided attention, the Interference condition of the CWIT required selective attention, and the Interference/Switching condition required both selective and divided attention.

In respect of attentional tasks in the 12 Gy subsample, Table 6 shows only a significant difference for the Block Design subtest, and Table 8 shows only a significant difference for the Word Reading condition of the CWIT. Contrary to expectation, Block Design scores in the 12 Gy subsample were above the norm, and the reasons for this superior performance have already been discussed. In contrast to the strong performance on the Block Design subtest, however, the 12 Gy subsample was significantly slower to complete the Word Reading condition of the CWIT. Although the effect size for this difference was small, reading is known to be an academic difficulty after treatment, and was reported as a major issue by one of the participants. The issue of reading therefore warranted further exploration. An important skill required for reading is visual tracking, which involves controlled eye movements in order to read from line to line. In considering the idea of visual tracking further, however, it seems unlikely that this would be the cause of the slow reading speed in the 12 Gy subsample, as no other significant differences were found for any other conditions of the CWIT, which also require visual tracking. Since Strauss and colleagues (2006) claim that reading is a skill that is fairly resistant to neurological insult, there must be another reason for a slow reading speed in the 12 Gy subsample, which may relate to educational factors. In particular, frequent absenteeism from school during treatment may be responsible for a slow reading speed, since reading is a skill that is acquired and developed in the classroom. This explanation seems more appropriate in light of the rest of the results. Had significant differences been found in other tests of visual tracking and visual scanning, such as the TMT, then the potential of a radiation-induced deficit would have been explored further. However, given the overall pattern of performance in the 12 Gy subsample,

the slow word reading speed seemed to relate to an underdeveloped academic ability and not to a radiation-induced attention deficit.

The situation was very different for the 18 Gy subsample, in which attention deficits were far more pronounced. In respect of attentional tasks, Table 12 shows significant differences for the Problems, Block Design and Pattern Completion subtests of the IS-A, and Table 14 shows significant differences for both parts of the TMT as well as all four conditions of the CWIT. In all cases, the performance of the 18 Gy subsample was significantly below that of the norm and the comparison group. A glaring commonality among all of the aforementioned tests is that they are timed cognitive tasks requiring speeded performance, which suggests that the attention deficits in the 18 Gy subsample are inextricably tied to a slowed processing speed.

In exploring the nature of the attention deficits, the large effect size for Problems, Block Design, and Pattern Completion indicates that sustained attention is a large part of the problem. In particular, poor performance in these three subtests implies that children treated with 18 Gy experience a great deal of difficulty maintaining focus on cognitive tasks pertaining to numerical reasoning and visuospatial processing. In terms of the other tests of attention, a small effect size was noted for both parts of the TMT, and a moderate effect size was noted for all four conditions of the CWIT. This is a blatant manifestation of executive function deficits, as the TMT and the CWIT are the most commonly used tests in the assessment of executive functions (Strauss et al., 2006). Moreover, Strauss and colleagues (2006) note that the TMT is a reliable indicator of neurological integrity, and the fact that the 18 Gy subsample performed poorly on both parts of this test suggests that participants may have some structural

damage in the brain. The damage is speculated to be in the area of the prefrontal cortex, which is responsible for executive functions. The significantly higher number of errors made in both parts of the TMT specifically implicates the anterior cingulate cortex, which is responsible for self-monitoring and enhancing attentional processes (Lezak et al., 2012). This is the second time the anterior cingulate cortex has appeared in the discussion (the first time being in the discussion on the anxiety level of the 18 Gy subsample). Its reappearance strengthens the reasoning that the increased anxiety in the 18 Gy sample may have a physiological basis. The significantly low performance throughout the TMT and the CWIT strengthens the argument for a sustained attention deficit in the 18 Gy subsample, as sustained attention was required to maintain focus for the duration of each task. There is, however, more to be found than merely a sustained attention deficit. This is because the capacity for sustained attention intrinsically impacts the capacity for selective and divided attention, which are the higher forms of attention required by TMT-B, as well as the Interference and Interference/Switching conditions of the CWIT (Sarter et al., 2001). Lezak and colleagues (2012) note that individuals who are slow on the Interference condition of the CWIT have difficulties with selective attention, as they struggle to sustain attention in the presence of distractors. They also have difficulties with inhibition, as the Interference condition requires the ability to ignore the irrelevant word and focus on the relevant colour (Marian & Shook, 2013). This information suggests that the 18 Gy subsample also had deficits in selective attention and inhibition. Individuals who are slow on TMT-B and the Interference/Switching condition of the CWIT have problems with divided attention and task switching, as the alternating tasks compete for cognitive resources until performance on one of the tasks eventually declines. Therefore, in addition to deficits in sustained attention, selective attention, and

inhibition, the 18 Gy subsample also showed deficits in divided attention and task switching. Cognitive decline in all of these processes is a clear indication of frontal lobe abnormalities, resulting in executive function impairment. However, one cannot ignore the effect of the increased level of anxiety on these cognitive processes. Eysenck and colleagues (2007) state that anxiety reduces the capacity for sustained attention and also impairs inhibition because anxious people are more susceptible to distraction by task-irrelevant stimuli. What is very interesting to consider at this point is the fact that all participants in this study were bilingual, and the bilingual brain is supposed to have better attention and task-switching capacities due to its developed ability to inhibit one language while using another (Marian & Shook, 2012). In fact, bilingual people have demonstrated superior performance on the Stroop test, because the Stroop test taps the capacity for inhibitory control (Marian & Shook, 2012). This was not the case in this study, where the bilingual participants demonstrated low performance on all four conditions of the CWIT. It suggests that the apparent frontal lobe abnormalities in the 18 Gy subsample, coupled with an increased level of anxiety, are powerful enough to completely override the bilingual advantage in respect of executive function tasks.

Interestingly, no significant differences were found in any of the RAVLT learning trials or in Digits Forward, suggesting that auditory attention is less affected by cranial irradiation than visual attention. The nonsignificant results for these two language-related tasks may also be due to the larger language-learning capacity of the bilingual participants (Marian & Shook, 2012). Although the Problems subtest is technically a verbal subtest and relies on auditory attention, the nature of this cognitive task places significant demands on cognitive resources. The mental

arithmetic that is required places high demands on working memory and processing efficiency. As such, it is believed that the low performance of the 18 Gy subsample on the Problems subtest is more an issue of working memory than an issue of simple auditory attention. This will be explored further in the discussion on working memory.

In general conversation with the participants, a frequently reported issue was a difficulty maintaining concentration in class. Interestingly, a research trial at the St Jude Children's Research Hospital found that survivors of childhood cancer benefited from a drug called methylphenidate, which is commonly used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (Conklin et al., 2010). Conklin and colleagues (2010) reported that survivors scored higher on tests of sustained attention approximately one year after starting the drug. Participants' school performance also improved because they were better able to plan ahead for projects and remember to hand in assignments (Conklin et al., 2010). The fact that child survivors of acute leukaemia benefit from ADHD medication confirms the existence of attention deficits after cranial irradiation.

In summary, there is strong evidence of attention deficits following 18 Gy of cranial irradiation. The impairment seems to originate at the basic functional level of sustained attention, and extends to the higher levels of attention, selective and divided attention. Problems with self-monitoring, inhibition and task switching were also identified in the attention tasks, further pointing to executive function deficits after 18 Gy of cranial irradiation. The significantly reduced capacity for attention in the 18 Gy subsample seems to cause problems in visuospatial tasks more than in language-

related tasks. The affected brain areas are believed to be the prefrontal cortex and anterior cingulate cortex. However, the increased level of anxiety in the 18 Gy subsample may also be responsible for the observed attention deficits. The fact that ADHD medication has proven to be beneficial in the paediatric leukaemia population confirms that the attention deficits in existence after treatment are real and worthy of further exploration. In contrast to the 18 Gy subsample, the 12 Gy subsample was relatively free from attention deficits. Their issue with word reading seems to be more a factor of education than a radiation-induced deficit.

5.3.2 Working memory

In order to address the question of working memory impairment after cranial irradiation, participants' performance on the Problems subtest of the IS-A, Digits Backward, TMT-B, as well as the Interference/Switching condition of the CWIT was considered. Since the working memory model contains the central executive, attentional control has a substantial role in working memory and cannot be separated from it. Eysenck and colleagues (2007) note that working memory has limited attentional resources, so the processing efficiency of working memory tends to decline with tasks that place significant demands on the central executive of working memory. The cognitive tasks of TMT-B and Interference/Switching are thought to place significant demands on the central executive, as participants have to switch attention between tasks.

In respect of working memory in the 12 Gy subsample, Table 6 shows no significant difference for the Problems subtest, and Table 8 show no significant differences for Digits Backward, TMT-B, or Interference/Switching of the CWIT. This leads to the

conclusion that the capacity for working memory remains intact after 12 Gy of cranial irradiation. This finding makes sense in the context that attentional processes were previously found to be intact in the 12 Gy subsample.

In the 18 Gy subsample, however, Table 12 shows a significant difference for the Problems subtest, and Table 14 shows significant differences for TMT-B and the Interference/Switching condition of the CWIT. The effect size was large for Problems, small for TMT-B, and moderate for Interference/Switching. The large effect size for Problems clearly points to a working memory deficit after 18 Gy of cranial irradiation, which was evident during the administration of the task. The frequent requests by participants to repeat items were not believed to relate to an auditory attention deficit. Rather, it became increasingly apparent that a single oral presentation of the item was insufficient for the participants to fully process the information and provide a correct answer. As items increased in complexity, so too did the frequency of incorrect responses, suggesting that participants experienced a great deal of difficulty holding all elements of the question in mind while simultaneously calculating the answer. The small and moderate effect sizes for TMT-B and Interference/Switching respectively point to the high demand of mental double-tracking on the central executive. As predicted by Eysenck et al. (2007), the processing efficiency of working memory decreased as more resources were invested to attain a given performance level in these executive function tasks. Additionally, Eysenck and colleagues (2007) note that distraction effects are greater when the cognitive task involves switching attention between tasks, which was the function tapped by the TMT-B and Interference/Switching. Given the sustained attention deficit previously identified in the 18 Gy subsample, it is not surprising that

participants had difficulty with the task switching tasks. Interestingly, Table 14 shows no significant difference for Digits Backward in the 18 Gy subsample. Although reverse sequencing operations rely on working memory, they do not place as many demands on the central executive as mental arithmetic and task switching. As such, the significantly low performance on the Problems subtest, as well as on the TMT-B and Interference/Switching task, reflects the increased task demands on the central executive, and performance on these tasks declined as attentional resources were depleted.

In summary, the inefficiency of working memory in the 18 Gy subsample was clear. This inefficiency related to the overloading of the central executive, which resulted in a reduced processing efficiency. In contrast, working memory was intact in the 12 Gy subsample. This finding was appropriate in light of the fact that attentional processes were intact in the 12 Gy subsample.

5.3.3 Processing speed

It is important to bear in mind that deficits in sustained attention and working memory are often caused by an underlying slowed processing speed (Lezak et al., 2012). In order to obtain a pure indication of processing speed, the researcher considered participants' performance on the Coding subtest of the WISC-R, a test of psychomotor speed.

Table 8 shows no significant difference in Coding performance between the 12 Gy subsample and the comparison group, indicating that psychomotor speed is intact after 12 Gy of cranial irradiation. This is an appropriate result for the 12 Gy

subsample, which exhibited average performance in all of the timed cognitive tasks, except for the Word Reading condition of the CWIT. The slowness in the Word Reading task is believed to be related to an underdeveloped reading skill rather than to a processing speed deficit. Table 14 shows no significant difference in Coding performance between the 18 Gy subsample and the comparison group. This is an anomaly for the 18 Gy subsample, which exhibited significantly slow performance on many of the timed cognitive tasks in the test battery. The anomaly possibly arose because Coding is primarily a test of psychomotor speed, which makes relatively few demands on executive functioning. Cognitive tasks such as the TMT and the CWIT are considered to be more challenging because speeded performance is more difficult to achieve in complex executive tasks than in simple psychomotor tasks. Therefore, it must be clarified that while 18 Gy of cranial irradiation does not seem to impact processing speed at a basic psychomotor level, it does tend to impact processing speed in cognitive tasks with a high level of complexity.

Interestingly, the most frequently reported complaint by participants and their parents/caregivers was slowness in class. Parents/caregivers reported that teachers perceive the child survivors as “slow learners” when they return to school. They often advise parents to move their child to a special needs school, which was the case with two of the participants in this study. A third participant was in the process of investigating the option of special needs schooling at the time of this study. This highlights the practical implications of the cognitive changes that are experienced after treatment.

In summary, processing speed in both the 12 and 18 Gy subsamples was unaffected for simple psychomotor tasks like Coding. However, at 18 Gy of cranial irradiation, processing speed tends to decline for complex executive tasks like the TMT and the CWIT. By contrast, children treated with 12 Gy are unaffected in the area of processing speed, even for complex executive tasks.

5.4 Memory and Learning

In order to answer the question of whether long-term memory deficits are present after treatment, participants' performance on the RAVLT and ROCFT was considered for verbal memory and visuospatial memory respectively.

5.4.1 Verbal memory and learning

Table 8 shows no significant differences for any trials of the RAVLT in the 12 Gy subsample. This suggests that verbal learning and memory are intact at lower doses of cranial irradiation. It also indicates adequate medial temporal lobe integrity in the 12 Gy subsample.

Similarly, no significant differences were found for the learning trials or the delayed recall trial of the RAVLT in the 18 Gy subsample, suggesting that verbal learning and memory remain intact even at higher doses of cranial irradiation. What is interesting, however, is that Table 14 shows a significantly higher score for RAVLT Learning Over Trials, which is the Total Learning score corrected for immediate verbal memory span (Trial 1). Even though the effect size for this difference was small, the higher score reflects the small immediate verbal recall span of the 18 Gy subsample,

since Learning Over Trials is calculated by subtracting five times the score for Trial 1 from the Total Learning score. The small immediate memory span points to an attentional control issue upon first exposure to the list-learning task. However, once correcting for Trial 1, verbal learning capacity proved to be a strength in the 18 Gy subsample, which may be attributable to the bilingual advantage in language learning (Marian and Shook, 2012).

In summary, verbal learning and memory seem unaffected at both 12 and 18 Gy of cranial irradiation, as indicated by Total Learning and Delayed Recall scores falling within the average range. The high score for Learning Over Trials in the 18 Gy subsample reflects their small immediate verbal memory span, which may be related to an attentional control issue upon first exposure to the list-learning task. However, once familiarity with the task increased, so too did performance. In support of Holland (2013), this suggests that verbal learning is relatively unaffected by cranial irradiation.

5.4.2 Visuospatial memory and learning

Table 8 shows no significant differences for either the copy or delayed-recall trial of the ROCFT in the 12 Gy subsample, indicating that visuospatial processing and visuospatial memory functions are intact at lower doses of cranial irradiation. Since the ROCFT also places high demands on executive functioning, the nonsignificant result confirms that executive functions are intact at 12 Gy of cranial irradiation.

On the other hand, Table 14 shows significant differences for both the copy and delayed-recall trials of the ROCFT in the 18 Gy subsample, which was characterised

by low performance. This confirmed the findings in Whitaker and Schutte's (2012) original study, in which significantly lower scores were found in both trials of the ROCFT in a sample of 8 children treated with 18 Gy of cranial irradiation. In the present study, the effect size was small for both trials, which is indicative of mild deficits in visuospatial processing and visual memory at higher doses of radiation. Holland (2013) believes that the visuospatial deficits that exist after cranial irradiation are caused by executive function deficits relating to poor planning and organisation. Performance on the ROCFT relies heavily on the ability to understand the gestalt, which is mediated by the right hemisphere (Lezak et al., 2012). In analysing the method of construction employed in copying the figure, the majority of participants relied on a detail-orientated analytic approach (see Table 23), which is the characteristic processing style of the left hemisphere (Devinsky & D'Esposito, 2004). Although the analytic approach is an acceptable approach, it suggests that participants failed to perceive the gestalt in figure. This may point to structural damage in the right hemisphere, making it slightly more difficult to integrate visual information in a holistic manner. As such, child survivors may rely more heavily on the organisational approaches of the intact left hemisphere, which could explain the use of the analytic approach in the ROCFT. The role of executive functions in visuospatial tasks may account for why visuospatial processing deficits tend to co-occur with executive function impairment in children irradiated with 18 Gy.

Holland (2013) claims that the relationship between the initial copy and the recalled figure is also an important consideration, in that an inadequate copy may predetermine visual memory deficits in the ROCFT. This is because long-term visual recall depends on the quality of encoding in working memory, which is why it is

important to take into account the adequacy of the initial copy when interpreting the delayed-recall score (Strauss et al., 2006). In the results of this study, the initial copy scores in the 18 Gy subsample were significantly low. This is indicative of difficulties with visuospatial attention and perception, as well as visual organisation (Holland, 2013). The production of a poor initial copy also suggests that encoding in working memory was inadequate (Strauss et al., 2006). This may be related to abnormalities in the right dorsolateral prefrontal cortex and right parietal lobe, which are both involved in encoding visual information in working memory. It also implicates the fronto-parietal network in the extent of the radiation injury, which is responsible for directing attention in respect of visuospatial tasks (Brinkman et al., 2012). Inadequate encoding in visuospatial working memory directly affects consolidation in long-term memory, which may explain why the delayed-recall scores were equally as poor as the initial copy scores in the 18 Gy subsample (Strauss et al., 2006). Therefore, it is believed that the visuospatial deficit in the 18 Gy subsample originates at the level of visual processing in working memory, which directly affects retrieval from long-term memory.

The obvious difference between RAVLT and ROCFT performance in the 18 Gy subsample is thought to reflect differences in grey matter versus white matter functioning. Anderson and colleagues (2008) claim that verbal learning is associated with deep grey matter structures such as the hippocampus; whereas visuospatial learning is associated with white matter tracts. The average performance of the 18 Gy subsample in the RAVLT (and also in other language-related tasks) suggests that grey matter is relatively resilient to the effects of cranial irradiation. On the other hand, the significantly lower performance in the ROCFT (and also in other visuospatial tasks)

illustrates the vulnerability of white matter tracts to cranial irradiation. Ultimately, the difference in RAVLT and ROCFT performance highlights the differential effects of cranial irradiation on white and grey matter functioning.

In summary, the 12 Gy subsample showed no evidence of long-term verbal or visuospatial memory deficits. This is likely due to the fact that the 12 Gy subsample had no issues with verbal and visuospatial processing in working memory. The fact that visuospatial functions are intact at 12 Gy of cranial irradiation also leads to speculation that lower doses of cranial irradiation cause fewer white matter abnormalities. By contrast, the 18 Gy subsample experienced a mild decline in visuospatial memory, which is thought to relate to inadequate visuospatial processing at the working memory level. Right hemispheric abnormalities have been suspected at 18 Gy of cranial irradiation, given the reduced capacity for holistic visual processing and increased reliance on the analytic processing of the left hemisphere. In contrast to the findings for visuospatial memory, verbal memory was unaffected in the 18 Gy subsample. This may be because verbal processing at the working memory level was intact. The differences in RAVLT and ROCFT performance clearly indicate the differential effects of cranial irradiation on white matter and grey matter in the brain.

In conclusion to this part of the discussion, which compared neuropsychological test performance between the two treatment subsamples, cognitive impairment at 18 Gy is much more profound than cognitive impairment at 12 Gy of cranial irradiation. The 18 Gy subsample was impaired in the domains of numerical reasoning, visuospatial processing, and executive functioning. By contrast, the 12 Gy subsample was only affected in the domain of word reading speed. An isolated deficit such as this does not

readily point to a radiation-induced deficit, as cranial irradiation is known to affect a number of neuropsychological domains. It is more probable that educational factors, such as underdeveloped reading skills, contributed to this result. Overall, the results clearly indicate a dose-effect relationship in respect of the cognitive impairment, which is in line with the literature stating that higher doses of cranial irradiation are associated with greater cognitive effects (Copeland, 1992).

5.5 The Neuropsychological Profile

In order to obtain a performance profile of a larger sample of participants, the researcher collapsed the two treatment subsamples into a single group. The profile obtained in Figure 1 represents the overall pattern of neuropsychological functioning after treatment with prophylactic cranial irradiation. However, given that the composition of the total sample was two-thirds 18 Gy and only one-third 12 Gy, the researcher cautions that the resulting profile is more representative of children irradiated with 18 Gy than of children irradiated with 12 Gy.

Figure 1 in chapter 4 shows that the performance of the total sample was low in almost every test. This highlights the unfortunate reality that there are almost no residual cognitive strengths after treatment with cranial irradiation. Table 20 shows that the significantly low performances were in respect of the copy and delayed-recall trials of the ROCFT, TMT-A and TMT-B (including errors), and the Colour Naming, Word Reading, Interference and Interference/Switching conditions of the CWIT. This suggests that visuospatial processing and complex executive functions requiring

speeded performance are negatively affected in children treated with prophylactic cranial irradiation.

In terms of visuospatial processing, the effect size for both trials of the ROCFT was small. Therefore, a real but mild decline in visuospatial processing exists after treatment, which points to inefficient encoding in working memory. The existence of a visuospatial working memory deficit may explain why the total sample also showed a mild deficit in visuospatial long-term memory, since encoding in working memory directly affects retrieval from long-term memory. It is speculated that right hemispheric abnormalities particularly in the region of the right parietal lobe exist after treatment with prophylactic cranial irradiation, which contributes to the visuospatial impairment observed in the total sample.

In terms of the executive tasks, the effect size was small for both parts of the TMT, moderate for the Colour Naming and Word Reading conditions of the CWIT, and small for the Interference and Interference/Switching conditions of the CWIT. This is indicative of mild to moderate executive function impairment in children treated with prophylactic cranial irradiation. It is speculated that frontal lobe abnormalities particularly in the region of the prefrontal cortex and anterior cingulate cortex exist after treatment with cranial irradiation, since executive functions rely heavily on these areas.

No deficits were found in intellectual functioning in the total sample, suggesting that general cognitive functions remain intact after treatment. Even though mild to moderate deficits in executive functioning were found, it is important to remember

that executive functions are a separate class of functions from general cognitive functions (Lezak et al., 2012). This means that intelligence can remain intact in the presence of executive function impairment, which was the trend observed in this study.

The neuropsychological profile produced in Figure 1 can also be used to contextualise Whitaker and Schutte's (2012) study findings. The impairment in right hemispheric visuospatial abilities that was found in the original study can now be qualified by relating it to an impairment in executive functions: Since the ROCFT places high demands on executive functions, one of the contributing factors to the visuospatial impairment may be an inadequate capacity to plan and organise the drawing in such a way as to produce a cohesive figure.

While the deficits found in the total sample were mostly mild in nature, Anderson and colleagues (2008) assert that the identification of even the subtlest deficits is helpful to both child survivors and clinicians in the paediatric leukaemia field. This is because the treatments for acute leukaemia are continually improving, and quality of life is becoming increasingly more important in light of modern day medical advances. As such, even findings of minor declines in cognitive functioning are important as they may help researchers in the development of treatments with fewer and fewer long-term toxic effects (Anderson et al., 2008).

In summary, the neuropsychological profile is characterised predominantly by mild cognitive weaknesses. Children treated with prophylactic cranial irradiation are typically affected in the domains of executive functioning and visuospatial

processing. This pattern of impairment leads to speculation that frontal lobe and right hemispheric abnormalities exist after treatment with cranial irradiation. Seeing as the deficits relate to the dorsolateral prefrontal cortex, anterior cingulate cortex, and parietal lobes, it is believed that the fronto-parietal network is most vulnerable to the effects of cranial irradiation.

5.6 Implications for Clinicians and Suggestions for Survivors

The discovery of a dose-effect relationship raises many considerations for clinicians in the paediatric oncology field, whose main objective is to improve the outcome of patients with as few long-term effects as possible (Meshinchi & Arceci, 2007). When faced with low risk patients, it is hoped that the results of this study may motivate radiation oncologists to irradiate with lower doses if at all possible in order to minimise long-term cognitive effects after treatment. However, clinicians are faced with a difficult dilemma when it comes to high risk patients, where, on the one hand, higher doses of treatment improve patient outcome but increase the risk for late cognitive effects; and on the other hand, lower doses of treatment may increase the risk of relapse and even death if inadequate in treating the leukaemia. Ultimately, when faced with high risk patients, clinicians have to opt for extremely intensive therapy to overcome resistant disease, prevent relapse and safeguard survival (Meshinchi & Arceci, 2007). In foreseeing this reality, the researcher has made some suggestions for survivors below.

It is important for parents/caregivers and teachers to remain vigilant of potential learning problems so that if they appear, help at school can be started immediately

(Keene & Oeffinger, 2001). The cornerstone warning signs of radiation-induced cognitive impairment include slowness in class and a reduced capacity to focus for prolonged periods of time. Children treated with cranial irradiation will need to develop compensatory strategies in order to effectively reintegrate into the classroom, and the sooner help can be started, the better the child will cope with the demands of mainstream school (Anderson et al., 2008). If the problem is identified too late or feels too big to be overcome, children may be referred to remedial schools. Instead of struggling in mainstream school, being in a learning environment that is conducive to the child's needs will improve the child's self esteem and provide many more benefits going forward, as the cognitive impairment may persist for many years after treatment. Parents/caregivers are therefore urged to search for the right educational environment for their child after treatment.

If survivors are overcome by the inability to maintain concentration in class, one way to ease the effect of attention deficits after treatment is to consider ADHD medication. Although this is a controversial subject for parents/caregivers, methylphenidate in ADHD drugs such as Ritalin and Concerta has been proven to benefit survivors in their school performance in the long run by helping them to better manage their tasks (Conklin et al., 2010).

When it comes to school learning, familiarity with schoolwork is critical to academic success. Lezak and colleagues (2012) believe that individuals who are slow to process new information still have the potential to achieve academically but only once they have become familiar with the new material (Lezak et al., 2012). They note that individuals with a slow processing speed are usually slow to respond to material that

is complex and unfamiliar, but their processing speed increases with increasing familiarity with the study material (Lezak et al., 2012). This is achieved through increased activation of the neural pathways in the brain. It is, however, extremely difficult to activate neural pathways that have been damaged by cranial irradiation, such as the pathways for numerical reasoning. As such, child survivors will need to develop compensatory learning strategies in order to cope with mathematical learning (Anderson et al., 2008). The analytic style of processing relied upon by the majority of the participants in this study reflects the need for child survivors to break down complex problems into smaller, more manageable parts. Fortunately, the pathways for verbal learning seem to remain intact after treatment. Therefore, child survivors should develop verbal learning strategies and direct their efforts at improving their academic performance in language-related subjects. Stronger academic performance in language-related subjects might help to improve their overall academic average and pass rate at school.

Remedial interventions should therefore focus on teaching survivors how to break down large complex problems into smaller, more manageable problems, and should also focus on developing verbal skills in child survivors. These interventions may help to build up an academic self-esteem that is lost through absenteeism from school during treatment and learning difficulties experienced after treatment.

5.7 Study Limitations

This study was not without limitations. Firstly, the sample was heterogenous in respect of the different types of acute leukaemia. While the 12 and 18 Gy subsamples

each contained a mix of ALL and AML diagnoses, it must be acknowledged that the different disease processes and different lengths of treatment may have had an underlying impact on cognitive test performance. Furthermore, the effect of intrathecal chemotherapy cannot be fully discounted, as this study did not contain a "chemotherapy only" treatment subsample. The reason for this was purely logistical, as children who received chemotherapy without cranial irradiation were too young to be included in this study.

Secondly, although the sample size in the present study was a vast improvement on the sample size in the 2012 study, it was still relatively small. This was limiting in that it did not lend itself to the more sophisticated statistical analyses that are often required by a data set with a reasonable number of confounding variables. While international studies enjoy larger sample sizes, the South African situation differs greatly in terms of the smaller number of cases diagnosed per year, and the late stage at which the leukaemia is often diagnosed. As a result, there is a limited paediatric leukaemia population in South Africa from which to draw a sample for research purposes. The researcher was therefore pleased to have obtained 20 participants between two major government hospitals in South Africa. However, splitting the sample according to radiation dosage led to an even smaller number of participants in each subsample. This was particularly limiting in the 12 Gy subsample, which comprised only 7 participants. As such, the 12 Gy subsample may not have been large enough to detect significant differences in cognitive test performance. In order to compromise for the small sample size, the researcher employed nonparametric statistical analyses and conducted fairly basic inferential statistics. The fact that results reached statistical significance in the 18 Gy subsample suggests that the

cognitive effects after cranial irradiation are real, and worthy of further exploration. While the researcher gave due consideration to more technical statistical techniques, this would have entailed manipulating the data in such a way which would have introduced unnecessary error and led to a confusing outcome. The researcher was satisfied that the results reflected what was stated in the literature and answered the research questions. In an effort to increase the power of the results, the researcher collapsed the treatment subsamples into a total sample. While the larger sample size of the total sample may have provided more powerful results, the observed differences seem to reflect those found in the 18 Gy subsample, as there were twice as many participants in the 18 Gy subsample than in the 12 Gy subsample. As such, the neuropsychological profile is more representative of children treated with 18 Gy and may not be meaningful to those treated with 12 Gy. The researcher acknowledges that numerous statistical analyses were conducted on the data, which increased the risk for familywise type I error; however, the use of numerous psychological tests allowed the researcher to identify patterns and trends in the data, which was an advantage in this study.

Thirdly, without baseline data, it was impossible to determine how participants' performance compared with their level of functioning prior to their disease. However, a pre-test was deemed inappropriate for a number of reasons, such as vulnerability at diagnosis and duration of treatment. Because the study design was not a true experimental design, a matched control group could not be used. The researcher had to make use of a comparison group from a current local study, which had a narrower age range than that of the treatment group. However, the comparison group was

comparable on all other demographic variables in this study, which is why it was selected as the most suitable reference group for this study.

Lastly, in terms of the generalisability of study findings, the strict inclusion criteria in place for this study mean that the findings can only be generalised to black African, low socioeconomic children in the paediatric leukaemia population of South Africa. They also only apply to children who were treated with cranial irradiation, and not to children who were treated with chemotherapy alone. Although the strict inclusion criteria limit the generalisability of findings, the purity of the sample increases the validity of the results in this study.

5.8 Directions for Future Research

Future studies should opt for a nation-wide approach and assess children in paediatric oncology units across the country in order to obtain the largest sample size possible. Perhaps then it may be possible to conduct statistical analyses not only based on radiation dosage but also based on type of leukaemia. For example, comparisons could be made between children with AML irradiated with 12 Gy versus children with AML irradiated with 18 Gy, and children with ALL irradiated with 12 Gy versus children with ALL irradiated with 18 Gy.

It would also be valuable to include a “chemotherapy only” treatment subsample so that the effects of intrathecal chemotherapy can be clearly defined and differences between treatment modalities can be observed. In order to include a “chemotherapy only” treatment subsample, participants would have to be long-term survivors (e.g. 10

years off treatment), as they would have been of a very young age at diagnosis. It is logistically quite tricky to find such participants, as they have been off treatment for so long and their contact details might be outdated. However, if at all possible, this would be a valuable subsample to include in a future study.

Although it is much better to compare participants to their own baseline condition, it would be unreasonable to suggest a longitudinal research design for this type of study given the length of treatment and the maturation effects that would occur during this time. Instead, a matched-pairs research design may be particularly useful, as it would provide the most closely representative comparison. The method of matching is a rather tricky one, however. The use of siblings is not the best idea because living with a sibling who is chronically ill can be a complicated issue. The healthy sibling may not receive as much attention from their parents/caregivers because all their attentional resources are allocated to the sick child, which may cause feelings of resentment or abandonment in siblings. One might consider using children who are chronically ill with a different disease; however, this is also not a good idea because of the differing disease processes and treatments involved. Given that absenteeism from school for prolonged periods of time was a confounding variable in this study, it would make sense to obtain a matched sample that has missed an equal amount of school as the treatment group. However, this would be difficult to achieve as healthy children are generally in regular attendance at school. The use of healthy children who are not regularly attending school taps into a whole different set of social problems, and this option should be avoided. In order to obtain a valid indication of the level at which participants in the treatment group should be performing, the best option would be to compare them to school-going children. The most appropriate

method would therefore be to match participants to healthy, school-going children, who share the demographic characteristics of their partner in the treatment group but who have no previous history of disease or long-term treatment. This sounds like a similar description of the comparison group that was used in this study; however, the comparison group was not intended as a matched-pairs design.

5.9 Conclusions

Evidence of mild to moderate cognitive impairment following treatment with prophylactic cranial irradiation has been found in this study. The affected domains are executive functioning and its associated processes of attention, inhibition, switching, working memory, and processing speed, as well as visuospatial processing. A dose-effect relationship emerged in the results, with 18 Gy of cranial irradiation associated with a wider spectrum of cognitive deficits than 12 Gy of cranial irradiation. These results support the literature stating that higher doses of cranial irradiation are associated with greater cognitive effects. The cause of the cognitive impairment is believed to be structural white matter abnormalities in the fronto-parietal network, although this would need to be confirmed by neuroimaging techniques, which were not available for this study. The researcher has suggested irradiating with lower doses wherever possible and preparing for early remedial interventions after treatment. The development of verbal abilities, the breaking down of complex cognitive problems into smaller, more manageable parts, and the possibility of ADHD medication have all been recommended to manage the learning difficulties that exist after treatment. These strategies may improve the quality of life for long-term survivors of paediatric

leukaemia, who may experience progressive cognitive decline for many years after treatment.

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Appendix A: List of Abbreviations for Figure 1

ABBREVIATION	PSYCHOLOGICAL TEST
BSCI_Y	BYI-II Self-concept Inventory
BAI_Y	BYI-II Anxiety Inventory
BDI_Y	BYI-II Depression Inventory
BANI_Y	BYI-II Anger Inventory
BDBI_Y	BYI-II Disruptive Behaviour Inventory
ISA_COMP	IS-A Comprehension
ISA_PROB	IS-A Problems
ISA_BD	IS-A Block Design
ISA_PC	IS-A Pattern Completion
ISA_ABS	IS-A Absurdities
ISA_SIM	IS-A Similarities
ISA_IQ	IS-A Abbreviated IQ
WISC_R_DF	WISC-R Digits Forward
WISC_R_DB	WISC-R Digits Backward
WISC_R_DT	WISC-R Digits Total
WISC_R_COD	WISC-R Coding
ROCFT_COPY	ROCFT Copy trial
ROCFT_DELAYED	ROCFT Delayed Recall trial
RAVLT_TOTAL	RAVLT Total Learning
RAVLT_DELAYED	RAVLT Delayed Recall trial
RAVLT_RECOG	RAVLT Recognition task
TMT_A_TIME	TMT-A speed
TMT_A_ERR	TMT-A errors made
TMT_B_TIME	TMT-B speed
TMT_B_ERR	TMT-B errors made
CWIT_CN_TIME	CWIT Colour Naming speed
CWIT_WR_TIME	CWIT Word Reading speed
CWIT_I_TIME	CWIT Interference speed
CWIT_I/S_TIME	CWIT Interference/Switching speed

Appendix B: Parental Information Sheet

Psychology Department

School of Human and Community Development

University of the Witwatersrand

Private Bag 3, WITS, 2050

Tel: (011) 717 4500 Fax: (011) 717 4559

Dear Parent/Guardian

My name is Sarah Whitaker and I am conducting research in the paediatric oncology unit in this hospital for the purpose of obtaining a Masters degree in Psychology at the University of the Witwatersrand. I would like to invite your child to take part in this study.

I am doing a neuropsychological assessment of children who were treated with radiation for leukaemia. The neuropsychological assessment will involve using standardised psychological tests to be able to describe your child's strengths and weaknesses pertaining to the way he/she thinks, remembers and learns.

If you, as the parent/guardian, agree to allow your child/ward to participate, he/she will be required to complete some activities, which include drawing tasks, working with patterns and blocks, repeating lists of words and numbers, solving number problems, identifying colours, as well as completing a questionnaire about his/her mood and emotions. These activities will be administered in a quiet room in the unit while you wait to see the doctor. The assessment may take about three hours to complete, with adequate time to rest in between. The tasks will be presented to your child in a non-threatening way, and no stress or discomfort will be caused in any way.

Participation is voluntary, and no individual will be advantaged or disadvantaged in any way for choosing to, or not to, participate. Please note that your child will be free to stop the procedure at any time and no negative consequences will follow.

Please be assured that confidentiality about the results between the researcher and your child is guaranteed. The children who participate will be assigned confidential numbers and any identifying information on the forms will then be destroyed to ensure the anonymity of your child. My research supervisor and I will be the only individuals who see the information gathered from the tests. No individual feedback can be given, as your child is on a managed treatment programme, therefore, upon request, the results will be supplied to the paediatric consultant in the unit to be used at their discretion. The data as a whole may be used in publications or conference presentations, but no data that identifies your child will be used. The information your child provides will be kept confidential for a period of 6 years following the completion of the project.

This research was approved by the Division of Paediatric Haematology and Oncology, by the CEO of the hospital and by the Human Research Ethics Committee

(Medical) at the University of the Witwatersrand. If you have any complaints, compliments or queries, you can address them to the HREC on 011 717 1234.

In order to facilitate the smooth running of this research, I would like to have your permission to access to your child's file at the hospital so as to obtain the duration, as well as type of treatment your child is currently on and any other treatments they have been on in the past.

Before we begin the assessment, you must sign the attached consent form in order for your child to participate in this study. Your child must sign the assent form. I will also ask you to complete a biographical questionnaire containing some questions regarding your child's background and development before we begin. **If available, please could you bring your child's last school report to their next appointment at the hospital.**

Should you have any further questions, please feel free to contact me or my research supervisor at the below mentioned telephone numbers, and we will be happy to assist.

Thank you and kind regards

Sarah Whitaker
Cell: 072 480 1540

Enid Schutte (Supervisor)
Cell: 082 920 6731

Appendix C: Parent/Guardian Consent Form

UNIVERSITY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development
Private Bag 3, Wits 2050,
Johannesburg, South Africa
Tel: (011) 717-4500
Fax: (011) 717-4559

Medical Ethics Number: M110436

I, _____, mother/father/legal guardian of

_____, give consent for my child/ward to participate in this study.

I understand that:

- Participation is voluntary.
- There is no risk or harm that could come to my child from taking part.
- My child or I may choose to stop the testing at any time, for any reason, with no penalty or loss of benefits.
- My child's results will remain confidential, and all information will be coded to ensure the anonymity of my child.
- No positive or negative consequences will follow from choosing to, or not to, participate.

By allowing my child to participate, I state that:

- My child has no history of epilepsy, meningitis, HIV infection, diabetes, serious head injury or previously diagnosed learning difficulty.
- All the relevant information about this research has been explained to me and my child clearly and simply, and I understand the information.
- The researcher has access to my child's file at the hospital in order to gain the demographic and medical information they may require.
- If available, I will give the researcher a copy of my child's last school report.

Signed: _____ Date: _____

Appendix D: Participant Assent Form

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

School of Human and Community Development
Private Bag 3, Wits 2050,
Johannesburg, South Africa
Tel: (011) 717-4500
Fax: (011) 717-4559

Medical Ethics Number: M110436

Hello

My name is Sarah and I am doing a research project in the hospital. I would like to invite you to take part in my project and help me explore the way your brain works.

If you would like to take part, then we will complete some activities together. I will ask you to make some drawings, remember some lists of words and numbers, work with patterns and blocks, solve some number problems, and answer some questions about the way you feel.

Your parents have agreed to allow you to participate but if you decide not to, that is okay too. No one will be upset or angry if you decide not to, or even if you decide to take part now and then later change your mind and want to stop.

You may ask me questions at any time, and if you have questions once I have left, you may phone me (Sarah) on 072 480 1540.

Would you like to take part in my project? *(Please tick **one** box)*:

Yes, I am willing to take part	
No, I do not want to take part	

Signing your name at the bottom of this form means that you agree to take part in this research project.

Thank you very much for your help.

Kind regards
Sarah Whitaker

Signature of child: _____ Date: _____

Appendix E: Biographical Questionnaire

Participant Information

Home Language:

Zulu		Sotho		Xhosa		English		Afrikaans		Other	

Handedness:

Right		Left	

Where does your child live? _____

Who is the person that takes care of your child most of the time? _____

Educational History

Name of child's school: _____

Current level of study in school (Grade 1-12): _____

Language of instruction at school: _____

Child's preferred language to speak in: _____

Academic position in class **before diagnosis**:

Above average		Average		Below average	

Academic position in class **currently**:

Above average		Average		Below average	

Has your child been absent from school regularly this year?

Yes		No	

If yes, please specify the reason and number of days absent on last two school reports:

_____

Has your child ever repeated a grade?

Yes		No	

If yes, which grade(s)? _____

Does your child experience any difficulties at school (socially, academically, etc.) or is your child anxious about anything in particular at school?

Yes		No	

If yes, please specify: _____

What does your child do when he/she gets home from school?

_____

Does your child participate in sport (at school or outside of school)?

Yes		No	

If yes, please specify: _____

Developmental History

Did the mother have any problems during her pregnancy with the child?

Yes		No	

If yes, please specify: _____

Were there any problems during the birth of the child?

Yes		No	

If yes, please specify: _____

Did your child learn to walk and talk around the right age?

Yes		No	

If no, please state reason: _____

Did your child attend crèche and pre-primary school?

Yes		No	

Does your child have any known learning disabilities or other neurological problems?

Yes		No	

If yes, please specify: _____

Has your child ever experienced any serious head injuries, for example, concussion, loss of consciousness or stitches?

Yes		No	

If yes, please specify: _____

Has your child ever received psychotherapy, physiotherapy, speech therapy, occupational therapy, had his/her eyes tested, or received any other forms of therapy?

Yes		No	

If yes, please specify when and for what reason(s):

_____

Other than leukaemia, has your child ever had any other serious diseases?

Yes		No	

If yes, please specify the disease and when diagnosed, treatment received and if still receiving treatment:

_____

Does your child have any difficulties with vision or hearing e.g. wears glasses/hearing aid?

Yes		No	

If yes, please specify: _____

Does your child suffer from any chronic pain?

Yes		No	

If yes, please specify: _____

Socioeconomic Information

Mother's highest education level: _____

Mother's occupation: _____

Father's highest education level: _____

Father's occupation: _____

Does your child receive a grant?

Yes		No	

Is there enough money at home to buy basic things like food/clothes?

Yes		No	

Is there enough money to buy expensive things (e.g. plasma TV)?

Yes		No	

Appendix F: Participant Treatment History

Participant number: _____

Inclusion Criteria	
Acute leukaemia	
Age 10 to 18 years old	
Cranial irradiation received	
Currently on maintenance treatment or off treatment	
No history of TBI, encephalitis, meningitis, stroke, HIV, diabetes or co-morbid conditions such as epilepsy, autism, downs syndrome	

D.O.B: _____ Current age: _____y _____m

Gender:

Male		Female	

Race:

Black		Coloured		Indian		White	

Diagnosis ALL / AML	Date diagnosed: Age at diagnosis:
Treatment protocol	
Full blood count at diagnosis	WCC x 10^9/L: Hb g/dl: Platelets x 10^9/L:
Chemotherapy	Date initiated: Off treatment:
Prophylactic cranial irradiation	Age at radiation: Date initiated: Date completed: Total dosage: Daily fractions: Treatment area: Field:
Current medication	For leukaemia: Any other chronic medication:
Current full blood count	WCC x 10^9/L: Hb g/dl: Platelets x 10^9/L:

Notes:

Appendix G: Letter of Permission from the Division of Paediatric Haematology and Oncology at the Charlotte Maxeke Johannesburg Academic Hospital

Division of Paediatric Haematology
and Oncology, Ward 294
Charlotte Maxeke Johannesburg
Academic Hospital
Private Bag X39
JOHANNEBURG
2000

Tel. No. : +27 11 488 3290
Fax No.: +27 11 488 4152/3967

OUR REFERENCE: WHITAKER.BG/sk
YOUR REFERENCE:

26 September 2012

TO WHOM IT MAY CONCERN

RE: SARAH-JANE WHITAKER
RESEARCH STUDY IN 294
POSTGRADUATE STUDIES IN PSYCHOLOGY MASTERS

Permission has been granted to Sarah to expand her research studies in the unit.

B.F. GOODWIN
CONSULTANT
PAEDIATRIC CONSULTANT

Appendix H: Letter of Permission from the Department of Paediatric Haematology and Oncology at the Chris Hani Baragwanath Academic Hospital

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

Chris Hani Baragwanath
Academic Hospital
Department of Paediatrics
Haematology / Oncology Unit
PO Bertsham 2013
Tel / Fax: (011) 933-9055

2nd August 2013

To whom it may concern

RE: Sarah-Jane Whitaker
Research Study in 44 OPD
Post Graduate Studies in Psychology Masters

Permission has been granted to Sarah to expand her research in the unit.

Dr. L. Wainwright
Head of Unit
Paediatric Haematology / Oncology

Appendix I: Letter of Permission from the CEO of the Charlotte Maxeke Johannesburg Academic Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. L. Mngomezulu
Tell: (011): 488-3793
Fax: (011): 488-3753
Date: 20th June 2013

Sarah –Jane Whitaker
Psychology Student
University of the Witwatersrand

Dear Student

RE: "Organizational styles, learning and memory in children receiving central nervous system prophylaxis for Leukaemia"

Permission is granted for you to conduct the above research as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Approved / ~~not approved~~

Dr. M.I. Mofokeng
Acting Chief Executive Officer

Appendix J: Letter of permission from the Division of Radiation Oncology at the Charlotte Maxeke Johannesburg Academic Hospital

Division of Radiation Oncology

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Department of Radiation Science
Medical School, 7 York Road
Parktown 2193, Johannesburg, South Africa

Tel: +27-11-481 2137
Fax: +27-11-481 2141
Email: vinay.sharma@wits.ac.za

Dated 24-4-2014

To whom so ever it may concern

This is to certify that Sarah- Jane Whitaker, a psychology student at University of Witwatersrand has been granted permission to undertake the project "A neuropsychological assessment of children treated with prophylactic cranial irradiation for Acute leukemia " in the Department of Radiation Oncology.

This project is being done for Masters of Arts in Psychology through University of Witwatersrand.

Vinay Sharma 24.4.2014

Prof. Vinay Sharma

Head, Department of Radiation Oncology

Appendix K: HREC (Medical) Ethical Approval

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)
Secretariat: Research Office, Room SH10006, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

University of the Witwatersrand, Johannesburg

03 April 2013

Ms Sarah-Jane Whitaker
School of Human & Community Development
Psychology Department
Umthombo Building
University

Sent by e-mail to: sjdwhitaker@gmail.com

Dear Ms Whitaker

RE: **Protocol M110436: 'Organisational Styles, learning and Memory in Children Receiving central Nervous system Prophylaxis for Leukaemia'**
Addendum

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has reviewed and approved your request to "look at the full neuropsychological profile of the leukaemic sample" on the abovementioned protocol, as detailed your letter dated 28 September 2012.

Thank you for keeping us informed and updated.

Please accept my sincerest apology for the delay in sending this to you.

Yours sincerely,

Anisa Keshav
Administrator
Human Research Ethics Committee (Medical)