Neuropsychological Profiles of Children and Adolescents with Craniosynostosis

By

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Declaration

This thesis does not incorporate without acknowledgement any material previously submitted for a degree in any University or other educational institution, and to the best of my knowledge it does not contain any material previously published or written by another person except where due reference is made in the text.

The research project was formally approved by the Ethics Committees of the Department of Psychology, Victoria University, and the Royal Children's Hospital, Melbourne, Victoria. The ethical principles and procedures specified have also been adhered to in the preparation of this report.

Annette Da Costa
August 2004

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Abstract

Craniosynostosis refers to the premature fusion of one or more cranial sutures, and typically occurs in utero. The major craniofacial disorders that feature craniosynostosis are the syndromic craniosynostoses, in which craniosynostosis occurs within a broader symptom complex (e.g. cardiac, respiratory and hearing impairments), and the nonsyndromic craniosynostoses, in which craniosynostosis presents in isolation. Reconstructive surgery to remodel the cranium is required in most cases, normally between 6 to 12 months of age.

The risks of adverse central nervous system and cognitive sequelae are well documented in these conditions. Whilst the syndromic craniosynostoses have historically been associated with varying degrees of intellectual impairment, the nonsyndromic forms have been regarded to have relatively benign cognitive sequelae. There is limited empirical literature addressing the long-term neuropsychological consequences of these disorders. Of that available, cognitive functions beyond global intelligence have seldom been examined, and no prior studies have comprehensively evaluated the wide array of cognitive skills that are important for adaptive functioning utilising standardised psychometric tools.

This cross-sectional study sought to address these gaps in the developmental literature on the craniosynostoses and comprehensively describe the neuropsychological profiles of 34 children and adolescents with syndromic (n=13) and nonsyndromic (n=21) craniosynostosis. Children of between 7 and 16 years of age (mean age 11 years) completed a battery of neuropsychological tests, measuring intelligence, attention, memory and learning, academic, executive and social and behavioural functioning.

Findings were consistent with existing literature in showing significantly lower intelligence in children with syndromic craniosynostosis (mean IQ=83.1, *SD*=21.9) in comparison to children with nonsyndromic craniosynostosis (mean IQ=103.4, *SD*=14.9) and their nonafflicted peers. Despite their lower mean intelligence, children with syndromic craniosynostosis displayed age-appropriate rote-style verbal and visual memory and reading skills.

Whilst of average intelligence, children with nonsyndromic craniosynostosis displayed cognitive profiles marked by mild to moderate deficits in attention and executive cognitive functions.

Measures of social and behavioural functioning yielded no clinically significant internalising or externalising problem behaviours in children with syndromic or nonsyndromic craniosynostosis.

Study findings challenge historical impression that has regarded the syndromic craniosynostoses as synonymous with intellectual disability. In addition, findings show that nonsyndromic craniosynostosis is not without functional repercussions; these children presented with cognitive features of organic dysfunction.

This research has broader implications for the management of children with craniofacial anomalies. Findings suggest that children with syndromic *and* nonsyndromic craniosynostosis require neuropsychological monitoring from early in their development, and extending into their school-age years. This will enable treatment interventions and management protocols to be formulated with greater precision, in order to optimise these children's developmental potential

Index of Abbreviations and Terms

Abbreviation	Full term
NSC	Nonsyndromic craniosynostosis. Also termed simple, isolated or secondary craniosynostosis. Craniosynostosis occurs in the context of no other related anomaly
SC	Syndromic Craniosynostosis. Also termed complex or primary craniosynostosis. Craniosynostosis occurs in the context of a broader symptom complex.

Term	Definition
Craniofacial	Pertaining to the cranium and the face.
Craniosynostosis	Premature closure of one or more cranial sutures.
Synostosis	Osseous union of bones that are normally distinct. Term used interchangeably with craniosynostosis
Craniosynostoses	Plural form to indicate a two or more conditions of craniosynostosis
Megalencephaly	Pathological parenchymal overgrowth of the brain.
Exopthalmos/ ocular proptosis	Marked protrusion of the eyeballs from eye sockets
Proptosis	Bulging of body organ or area
Hypertelorism	Abnormally wide space between two organs or parts (e.g. between eyes)
Hypotelorism	Abnormally small space between two organs or parts (e.g. close-set eyes)
Palpebral fissures	Opening between the margins of the upper and lower eyelids
Ptosis	The eyelid/s droop. Causes include weakness of the levator muscle
Canthus/ Canthi	Corner of the eye/s; the angle at the lateral/ medial margins of the eyelids.

Introduction

The Concept of Craniosynostosis

Of the human skull's many functions; it's largest component, the cranium, which comprises the dome-shaped vault and the cranial base, protects and insulates the brain. Growth and development of the skull vault and central nervous system are closely interrelated. The skull is dependent on the forces of brain growth to expand, and conversely, the brain requires the skull to accommodate growth, particularly during its most rapid growth phase; within the pre- and post-natal period.

Abnormalities of skull growth can result in significant distortions to its shape. Due to the close relationship between skull and facial bone growth, visible deformities of the face may also ensue. This combination of features is often referred to as craniofacial anomalies or craniofacial disorders. Of perhaps greater significance than the cosmetic sequelae of craniofacial anomalies, are the implications of this condition upon central nervous system growth and development. Skull growth impairments can limit and distort the normal pattern of cerebral growth and maturation, potentially resulting in significant cognitive impairments.

In this thesis, the influence of skull growth abnormalities occurring during the prenatal period will be examined with respect to the implications for long-term neuropsychological outcomes in affected children. One such craniofacial disorder, craniosynostosis, will be specifically addressed within this context. Craniosynostosis refers to the premature fusion of one or more of the cranial sutures, and affects one in 2500 newborns. It is a disorder which requires multidisciplinary assessment and treatment by craniofacial surgeons, neurosurgeons, psychologists, dentists, speech pathologists, and physiotherapists. Despite the potential implications of this serious abnormality for cognitive development, there is a paucity of literature that has addressed the neuropsychological features of these conditions, particularly with respect to long-term developmental outcomes. This research was an initial exploratory study aimed at providing a detailed characterization of the neuropsychological profiles of children and adolescents with various types of craniosynostosis.

Chapter One of this thesis will describe normal and abnormal skull growth, and its interrelationship with central nervous system formation and maturation processes. Abnormal skull growth due to craniosynostosis, and the potential implications of this pathological process for brain growth and development, will be discussed.

The etiological and clinical phenotypic and characteristics of the primary diagnostic disorders that feature craniosynostosis are described in Chapter Two. Prevalence rates, neurological and molecular characteristics of these conditions are also detailed.

In Chapter Three, the potential implications of craniosynostosis for central nervous system development and its related cognitive processes will be discussed. The developmental neuropsychological literature will be addressed within this context.

A critical evaluation of the psychological and neuropsychological literature on the craniosynostoses is presented in Chapter Four. The rationale, aims and hypotheses for the current research study are then presented.

Chapter Five describes the research design of the present study. \Sample characteristics, materials and procedures are detailed.

The results of data analyses are presented in Chapter Six. Firstly, the diagnostic groups of interest are compared on measures of intelligence, information processing, memory and learning and attention and executive functioning. Comparisons with normative population data are made for each of these domains. Secondly, the diagnostic groups are compared on social and behavioural functioning variables. Finally, four case studies, that illustrate the cognitive diversity that characterises the craniosynostoses, are presented.

In the final Chapter of this thesis, findings of the current study are interpreted, and discussed within the context of the previous literature on the psychological and neuropsychological characteristics of the craniosynostoses. Future research directions are explored, and recommendations made for the multidisciplinary management protocols of the craniosynostoses.

Chapter One

Normal and Abnormal Cranial Growth and Development

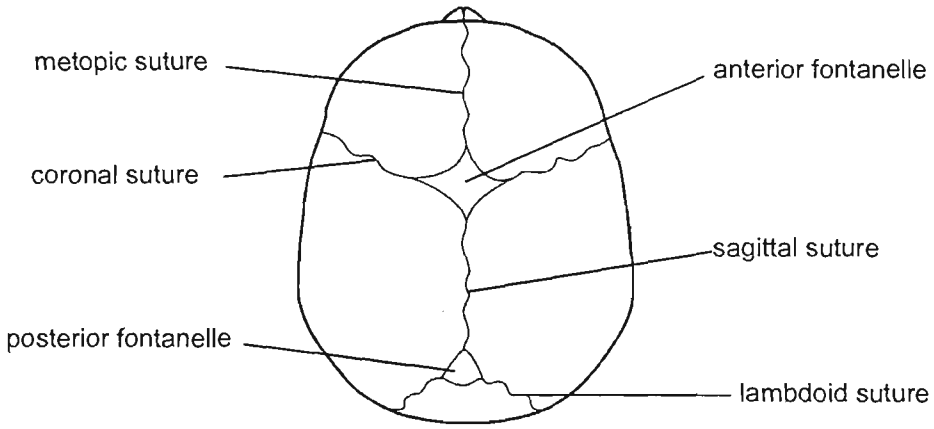
In this chapter, normal and abnormal skull growth, and its interdependent relationship with the central nervous system will be discussed. Abnormal skull growth due to craniosynostosis and the potential implications of this process for brain growth and development will then be described.

1.1 Normal Cranial Growth and Development

1.1.1 Calvarial bones, sutures and fontanelles

An infant's skull is composed of six separate cranial bones; the frontal, occipital, two parietal and two temporal bones. These bone plates are held together by strong fibrous, elastic tissues called cranial sutures. Between the bone plates and within the fibrous tissues are spaces, or openings, called fontanelles. The cranial sutures and fontanelles function as 'hinges' for the calvarium, permitting considerable flexibility during childbirth, as well as during the period of rapid growth of the skull and brain perinatally. Figure 1-1 depicts a normal infant skull with intact cranial sutures and cranial bones

Figure 1-1 Normal infant skull showing cranial sutures and fontanelles



1.1.2 Bone formation and growth

The cranial vault is comprised of a complex arrangement of predominantly membranous bones; that is bones that ossify directly. Formation of the cranial vault occurs at two sites during embryonic development; on inner and outer bone surfaces and at the cranial sutures. Enlargement of whole bones occurs from bone growth activities at the cellular level by a series of 'remodeling' movements throughout all inner and outer bone surfaces. There is simultaneously a movement of a whole bone by a 'displacement' process. The cranial sutures are situated between the cranial bones, and form the site from which the displacement proceeds. Growth of the cranial base is relatively slower and less expansive than that of the cranial vault. Bone deposition at the separated edges together with some intercellular growth contributes to an increase in its size. Disruption to the normal bone growth processes of the skull vault or cranial base may lead to wide variations in the skull and facial form. Whilst abnormalities of facial bone growth occur due to craniosynostoses, the focus of this thesis, due to the close interdependent relationship between skull and brain growth, is however, on the cranial vault.

1.1.3 Cranial Sutures and Fontanelles

Formally, Gray's Anatomy defines a suture as "an articulation in which contiguous margins of adjacent bone are united by a thin layer of fibrous tissues" (Goss, 1959). Cranial sutures are formed during mid-to-late gestation, and comprise fibrous bands of tissue that are created when the cranial bone fronts enlarge, move closer together, and either abut or overlap.

The major cranial vault sutures of the human skull are the *metopic* suture, which separates the frontal bones; the *sagittal* suture, situated between the parietal bones and extending from the anterior fontanelle to the posterior fontanelle; the paired *coronal* sutures running transversely between the two frontal and two parietal bones, and the paired *lambdoid* sutures, situated between the occipital and parietal bones. The minor sutures are the squamosal, located between the parietal, temporal and sphenoid bones and the sphenofrontal suture, which forms the continuation of the coronal suture into the cranial base (see Figure 1-1).

Cranial sutures serve as the principle site of bone growth as well as the major sites of skull expansion, exerting forces on the neurocranium in response to the growing

brain. To permit normal bone growth and room for the rapidly growing brain, the cranial bones must remain separate, and hence sutures need to remain patent, or open pre- and postnatally. This flexibility permits brain growth without constriction, whilst protecting the brain from minor impacts to the head.

The timing and course of cranial growth follows the neural growth curve; that is, it is most rapid during the first year of life, with most growth completed by two years of age, but slowing down dramatically between six to sixteen years of age. Fusion of cranial sutures normally commences by two years of age, but varies widely depending on the sutural location. The metopic suture normally closes first, within the first two years of life. Obliteration usually occurs next in the lower part of the coronal suture, followed by the posterior part of the sagittal suture and the lambdoid sutures. These and other sutures, including the 'minor' squamosal, occipitomastoid and sphenotemporal sutures normally fuse during the second and third decades of life. Smaller sutural growth adjustments, however, also occur to adult age.

The normal human skull also has six fontanelles, which are situated at the corners of the paired parietal, occipital and frontal bones, and which close on their own as part of normal cranial growth. The posterior and anterolateral fontanelles are obliterated within two to three months perinatally. The posterolateral fontanelle typically closes about the end of the first year and the anterior fontanelle is the last to close, about the middle of the second year.

1.1.4 Cerebral and Craniofacial Growth: interrelationships

Skull and brain growth are interdependent; the growth of the brain induces skull growth in a homogeneous and symmetrical fashion. The rapid development of the brain during the first year of life, which increases in size from 335gm to 925gm, reaching 80% of its adult size, influences and sets the pace for the moulding and shaping of the skull. In terms of the mechanisms of this process, as the cerebral and cerebellar hemispheres grow, the calvarial bones are drawn outward, in part, by the expanding meninges. As these membranes grow ahead of the expanding brain, the bones are carried (displaced) with them. The internal pressure exerted by the growing brain upon the inner table of the cranial plates determines the rate and form of neurocranial growth until late adolescence.

1.2 Abnormal Craniofacial Development

1.2.1 Craniosynostosis- Defined

Craniosynostosis is a universal phenomenon. It is a pathological process, which, as stated above, refers to the bony union of one or more of the cranial sutures before the normal time of closure. Craniosynostosis is primarily a condition of the infant and young child. It is typically of prenatal onset, although can occur following birth, and is identifiable by the characteristic abnormalities in head shape.

1.2.2 Birth Prevalence of Craniosynostosis

The best general estimates of the birth prevalence of craniosynostosis are those of metropolitan Atlanta, of 343 per 1,000,000 live births (Lanmer, Cordero, Wilson, Oimette, & Ferguson, 1987) and France (476 per 1,000,000 live births; Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac, & Renier, 1995; Lajeunie, Merrer, Bonaiti-Pellie, Marchac, & Renier, 1995). Other estimates have varied between 343-476 per 1,000,000 new births (M. M. Cohen & MacLean, 2000; Fryburg, Hwang, & Lin, 1995; Hennekam & Van den Boogaard, 1990; Lajeunie, Le Merrer et al., 1995; Lajeunie, Le Merrer, Marchac, & Renier, 1998; Lajeunie, Merrer et al., 1995; Renier, Lajeunie, Arnaud, & Marchac, 2000). In Australia, David, Poswillo, & Simpson (1982) estimated this as 0.25/ 1000 in their South Australian series of craniofacial patients.

However, true birth incidences may be hard to establish and can vary enormously. This reflects the different systems in terminology and variations in selection of case material. As well, minor cases may not present for medical attention. Treatment factors also vary considerably in different communities; medical views on the importance of the condition, changing aesthetic fashion, economic pressures and availability of specialist services likely influence referrals.

1.2.3 Impact of Craniosynostosis on Skull Development

When a suture is fused, there is no growth in a plain perpendicular to the line of the fused suture. With certain exceptions, notably the metopic and mendosal sutures, calvarial sutures which close prenatally and in infancy, are abnormal. Premature sutural fusion has very real significance in terms of the dynamics of abnormal

craniocerebral growth (David et al., 1982). The loss of sutural growth in the major sutural sites (e.g. metopic or sagittal) results in a relatively unyielding cerebral capsule, which fails to respond to the normal forces exerted by the expanding brain. It leads to disproportionate growth of the cranial bones and abnormal compensatory skull expansion throughout the head (Enlow, 1986), consequently resulting in characteristic abnormalities of head and facial shape.

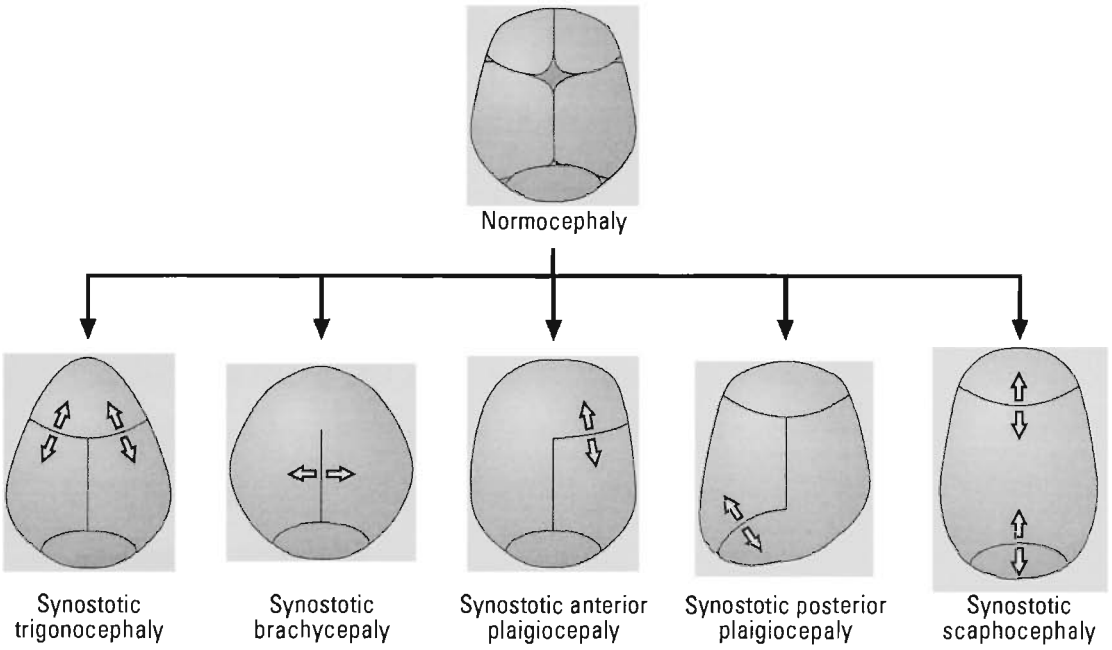
The shape and severity of the skull deformity in craniosynostosis is determined by the site of sutural fusion, as well as the order and rate of progression of synostosis (M.M. Cohen, 1979, 1975). The earlier the onset, the greater the effects on skull shape (M.M. Cohen, 1986). For example, the metopic suture separating the frontal cranial bones normally ossifies during the second postnatal year. The implications of premature synostosis of this suture upon anterior cranial growth and development of the underlying cerebrum will differ from that of the early fusion of the sagittal suture, given that the middle cranial fossae continues to grow several years after the growth of the former has ceased. Craniosynostosis of the minor sutures, such as the squamosal and sphenofrontal sutures, typically occurs without the dramatic morphological changes seen when the major sutures are affected, and as such, are not the emphasis of the current thesis. The potential implications of craniosynostosis for central nervous system growth and development and its associated cognitive processes are addressed in detail in Chapter 3.

1.2.4 Diagnostic Classification

Craniosynostosis may occur in isolation, as in the 'nonsyndromic' craniosynostoses, or as part of a wider constellation of symptoms, as in the various 'syndromic' forms of the disorder. Appendices A and B outline the most commonly utilized terminology and clinical phenotypic characteristics for the various diagnostic subtypes of the nonsyndromic and syndromic craniosynostoses. The primary diagnostic conditions that feature craniosynostosis will be described in detail in Chapter Two.

The most common craniofacial abnormalities due to craniosynostosis have been depicted in Figure 1-2.

Figure 1-2 Craniofacial Growth Patterns in Craniosynostosis



1.3 Pathogenesis and Aetiology of Craniosynostosis

Multiple hypotheses and etiological explanations have been put forth to explain the developmental pathogenesis of craniosynostosis.

1.3.1 Theoretical Perspectives on the Pathogenesis of Craniosynostosis

Otto (1830) first recognised the discrete clinical entity of fused cranial sutures, and coined the term craniosynostosis. However, it was the work of Rudolf Virchow (1851) that gave the concept wide currency. According to "Virchow's law", premature fusion of a suture results in inhibition of growth in the direction perpendicular to that suture. Virchow furthermore contended that compensatory skull growth also occurred in a direction parallel to the fused suture; resulting in an overexpansion of the cranium at open sutural sites to accommodate the growing brain. Hence, premature fusion of the sagittal suture along the midline of the skull would produce narrowness across the skull's width, with increased growth in an anterior-posterior direction.

With respect to the underlying pathogenesis of craniosynostosis, a popular theory has implicated a primary malformation of the cranial base, which results in the sequential malformation of the cranial sutures (Moss, 1959, 1975). Moss (1975) proposed that the dura, acting as a "messenger", carried an abnormal signal from the cranial base to the calvarium. Alternately, Park and Powers (1920) postulated a primary defect of embryonic tissue development led to both craniosynostosis and an abnormal cranial base, a view supported by the histopathologic studies of Burdi, Kusnetz, Venes, & Gebarski (1986), and clinical observations of Woon, Kokich, Clarren, & M. M. Cohen, 1980). Others, such as Albright & Byrd (1981) suggest that some cases of craniosynostosis are due to premature deposition of bone tissue of the calvarial plates at the calvarial sutures. David et al., (1982) has more broadly implicated disturbed growth of the entire cerebral capsule as contributing to the individual deformities associated with craniosynostosis.

As clinical interest in skull malformations intensified, it became evident that some of the more severe cases of craniosynostosis were associated with other congenital defects. This notion of craniosynostosis as a feature of a wider symptom complex

came with the clinical observations from Crouzon and Apert in the early 20th Century. Apert described associations of craniosynostosis with syndactyly, or fusion of the digits of the hands and feet (Apert, 1906). Crouzon (1912) described a familial syndrome of craniofacial malformations with protruding eyes. The work of these clinicians led to the recognition that in some cases, the abnormal development of the skull and face can present with other defects, constituting the respectively named conditions, Crouzon and Apert syndrome. These and other craniofacial conditions will be discussed in detail in Chapter two.

1.3.2 Aetiological Mechanisms

1.3.2.1 Genetic and Chromosomal Factors

Although the large majority of cases of craniosynostosis occur as "fresh" mutations in otherwise normal individuals, evidence for a genetic role has been indicated by the repeated observations of familial instances of the condition. Overall, 8% of all craniosynostosis pedigrees are familial (n=175 pedigrees; M.M. Cohen & MacLean, 2000), with both autosomal dominant and autosomal recessive modes of inheritance identified (M. M. Cohen, 1986).

A major breakthrough in understanding the genetic underpinnings of craniosynostosis has been the identification of genetic defects in several syndromes, including the three most common: Apert, Crouzon and Pfeiffer syndromes. Mutations in a group of genes coding for fibroblast growth factor receptor (FGFR), which regulate cell growth and bony proliferation (Muenke & Schell, 1995) and function in limb development have been implicated in craniosynostosis (Muenke et al., 1994; Reardon et al., 1994). As yet, however, the effector link between the chromosomal defect and the actual premature fusion is not fully understood.

1.3.2.2 Mechanical and extraneous causes

Some writers have postulated antenatal mechanical causes for craniosynostosis, such as intrauterine cranial compression (Graham, deSaxe, & Smith, 1979). Teratogens, for example drugs such as aminopterin have been linked to a malformation of which craniosynostosis can be a part (Shaw & Steinbach, 1968). Craniosynostosis also appears in biochemical disorders, such as rickets (Reilly,

Leeming, & Fraser, 1964), hyperthyroidism (Robinson, Hall, & Munro, 1969)and haematological conditions (Gooding, 1971).

Failure of brain growth has also been implicated in craniosynostosis. This is seen in microcephaly, where arrested brain growth may result in insufficient forces to expand the cranial bones resulting in a disproportionately small head. Craniosynostosis is also often seen where severe hydrocephalus has been treated with a low-pressure shunt (Andersson, 1966; Roberts & Rickham, 1970). These conditions represent secondary craniosynostosis, i.e. craniosynostosis as secondary to other causes, and are not considered within the context of the current thesis.

In summary, the actual pathological and aetiological mechanisms of craniosynostosis, although incompletely understood, do appear heterogeneous in nature. Animal experiments and a recent interest in molecular biology have pointed to the role of the dura and the underlying brain as taking credence over theories that incriminated the cranial base and the cranial sutures. Genetic factors are also becoming increasingly recognised.

1.4 Treatment of Craniosynostosis

Over the past decades, it has become accepted clinical practice to treat craniosynostosis by surgical excision of the fused cranial suture/s, and reshaping of the cranial vault. Cranial reconstructive surgery involves artificially dividing the cranial bones, and removing, remodeling and repositioning cranial bone segments; there is usually no penetration of the dura in this procedure. Figure 1-3 provides a diagrammatic representation of cranial vault reconstruction surgery for sagittal synostosis. The extent of bone removal and reshaping naturally varies according to the region of synostosis, although almost all instances involve reconstruction of the frontal skull region, extending anteriorly from the site of the coronal sutures.

Cranial vault remodeling is designed to improve craniofacial function and form; it secures greater freedom for the expansion of the brain, and should ideally eliminate the risk of future neurologic and cognitive impairment associated with increased ICP and inadequate brain growth capacity. Normalisation of craniofacial shape has aesthetic benefits, which are relevant considerations in terms of fostering a child's psychosocial development.

Figure 1-3 Cranial vault reconstruction surgery for sagittal synostosis

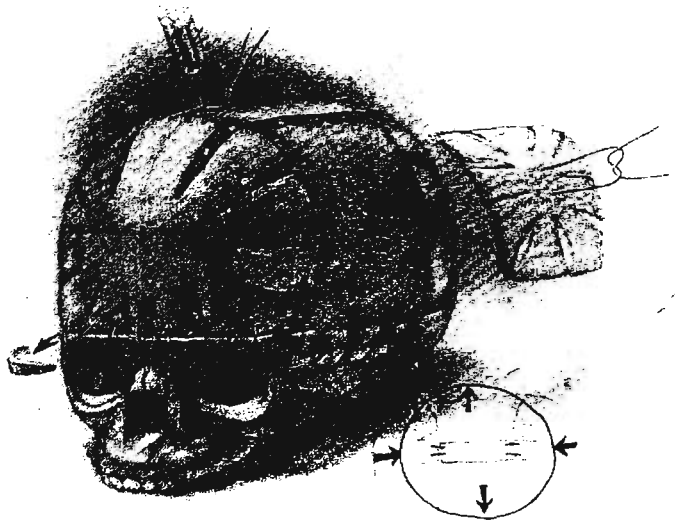


Diagram to show removal and remodeling of cranial bone segments to achieve a reduction in the anterior-posterior skull length.
Note. From *Craniosynostosis: Diagnosis, Evaluation and Management* (p. 215), by M.M. Cohen & R. MacLean, 2000, 2nd edition, New York: Oxford Uni Press. Copyright 2000 by Oxford Uni Press Inc. Reprinted with permission.

Because the shape of the skull is dependent on brain growth, the best cosmetic and functional results are obtained with earlier surgery; thus cranial vault reconstruction is ideally performed within the first year of life (Enlow, 1975). Cranial vault remodeling often needs to be repeated to accommodate changes in skull growth over time. The disorders of Apert, Crouzon and Pfeiffer syndromes often include severe growth disturbances of nearly all of the craniofacial regions, including the cartilaginous cranial base, the orbits, and the midface. In these cases, multiple surgical procedures can be expected over the course of the individual's development to normalise the craniofacial growth pattern. Multiple operative procedures to release fused of fingers and toes in Apert syndrome are also required.

Chapter Two

2 The Craniosynostoses: Etiologic and Clinical Phenotypic Characteristics

Craniofacial anomalies refer to visible deformities of the skull and face, and occur due to the pathological mechanism of craniosynostosis. In this chapter, the prevalence, clinical manifestations and neurological characteristics of the most recognised craniofacial disorders, in which craniosynostosis features as a primary characteristic, will be described.

2.1 Distinction between Syndromic and Nonsyndromic Craniosynostoses

There are two distinct groups of craniosynostosis conditions. The 'syndromic' craniosynostoses are also termed 'complex' or 'primary' craniosynostoses in the literature. The nonsyndromic craniosynostoses are variably referred to as 'simple' or 'isolated' craniosynostoses. These diagnostic groups can be delineated on the basis of a number of defining clinical characteristics:

1) The craniosynostosis in the nonsyndromic craniosynostoses typically presents in isolation, whereas that of the syndromic craniosynostoses occurs in the context of a wider symptom complex (e.g. limb defects, respiratory difficulties, cardiac and gastrointestinal problems, cleft lip and/ or palate).

2) The skull deformities of the nonsyndromic craniosynostoses primarily involve abnormal development of the upper portion of the skull (calvarium). Whilst only one sutural site is typically affected, multisutural involvement may also occur. In contrast, syndromic craniosynostosis entities are usually accompanied by multisutural involvement, as well as distortions of the cranial base and facial bone structures. Facial abnormalities of some significance are, however, sometimes observed in the simple calvarial deformities.

3) The sutural fusion and corresponding skull deformities in the craniofacial syndromes is almost always more extensive than that seen in the nonsyndromic craniosynostoses.

2.2 Genetic Factors

2.2.1 Syndromic Craniosynostoses

Syndromic craniosynostosis is caused by sporadic mutations representing new cases, as well as by familial transmission. All are transmitted in an autosomal dominant fashion and associated with a high degree of penetrance and variable expressivity (M.M. Cohen, 1979); such that the clinical manifestations of the syndrome in affected offspring occur with varying degrees of severity. Both male and female offspring are equally affected.

A major breakthrough in the understanding of the genetic underpinnings of craniosynostosis has been the identification of genetic mutations in several syndromes, including the four most common: Crouzon, Apert, Saethre-Chotzen and Pfeiffer syndromes. The same mutation in a group of receptors known as fibroblast growth factor receptors (*FGFR's*) which regulate cell growth and bony proliferation, and whose functions involve limb development are now clearly established, and found to result in different clinical conditions.

In Apert syndrome one of two fibroblast growth factor receptor 2 (*FGFR2*) gene mutations involving amino acids Ser252Trp and Pro253Arg has been found to cause the condition in nearly all patients studied (Wilkie et al., 1995). Crouzon syndrome is caused by multiple mutations in the *FGFR2* gene (Reardon et al., 1994). Some of the mutations seen in Pfeiffer syndrome are identical to that seen in Crouzon syndrome, highlighting the clinical overlap between the conditions. Mutations causing Pfeiffer syndrome have been found on the *FGFR1* (Muenke et al., 1994) and *FGFR2* genes (Lajeunie, Le Merrer et al., 1995), with the latter associated with a more severe clinical picture (Lajeunie, Le Merrer et al., 1995). TWIST gene mutations have been identified in Saethre-Chotzen syndrome (El Ghouzzi et al., 1997).

2.2.2 Nonsyndromic Craniosynostoses

Whilst most cases of isolated synostosis are sporadic, some familial cases are known, implicating a genetic aberration. Studies indicate familial prevalence of 14.4% in coronal synostosis, 6% in sagittal conditions and 5.6% in metopic synostosis (Fryburg et al., 1995; Hennekam & Van den Boogaard, 1990; Lajeunie,

Le Merrer et al., 1995; Lajeunie et al., 1998; Lajeunie, Merrer et al., 1995). Familial lambdoid synostosis is rare (Fryburg et al., 1995). Recent research has identified a single *FGFR3* gene mutation in both sporadic and familial nonsyndromic coronal craniosynostosis (Bellus et al., 1996; Gripp et al., 1998; Moloney et al., 1997).

2.3 The Syndromic Craniosynostoses

Over 90 syndromic craniosynostosis disorders are recognised in the literature. Several reviews are available, the most exhaustive being that of (M.M.Cohen, & MacLean, 2000). The most common of these encountered in clinical practice are Crouzon, Apert, Saethre-Chotzen and Pfeiffer syndromes, with the other craniosynostosis syndromes less often seen and less easily recognised. With all the craniosynostoses, the nature and timing of sutural closure determines the severity of the craniofacial malformations.

The following section describes those syndromic craniosynostoses that are represented in the present research study. A summary of the clinical features of these conditions is presented in Appendix A. In figures 2-1 to 2-5, three-dimensional computed tomography (CT) craniofacial imaging scans, x-ray and computed tomography magnetic resonance imaging (MRI) brain scans have been presented for the major syndromic craniosynostoses discussed below.

2.3.1 Crouzon syndrome

2.3.1.1 Prevalence

Described by Crouzon in 1912, this is the commonest craniofacial syndrome. (Martínez et al., 1991) estimated the birth prevalence of Crouzon syndrome to be 15.5 in 1,000,000 livebirths. Incidence rates have varied from 6.8% in Bertelsen's Danish patient sample (Bertelsen, 1958) to nearly 15% in the South Australian series of David et al., (1982).

2.3.1.2 Clinical Presentation

Crouzon syndrome involves a variety of calvarial and facial deformities, and is expressed in varying degrees of severity (Kreiborg & Jensen, 1977). Craniosynostosis usually affects the anterior portion of the skull and is combined

with underdevelopment of the midface. The coronal and sagittal sutures are affected in most cases (brachycephaly), although the synostosis is frequently progressive, and all major calvarial sutures eventually undergo fusion. Like all the syndromic craniosynostoses, whilst the shape of the skull varies depending on the sequence of sutural fusion, most often, the calvaria is short, with a high, steep forehead and a prominent bulge at the site of the anterior fontanelle in Crouzon syndrome. Skull base abnormalities occur, including underdevelopment of the entire anterior fossae (David et al., 1982). The jaw (maxilla) may be underdeveloped, which may produce an airway obstruction. As eye development is normal, due to relative orbital underdevelopment, the eyes literally 'grow out' of the facial skeleton, a condition which is usually a very noticeable feature of Crouzon syndrome. The eyes may be widely spaced (hypertelorism) and the nose stands out prominently. The palate of the mouth is high and narrow and the facial distortions compromise speech output. Aural abnormalities resulting in conductive hearing loss and middle ear disease may also occur.

2.3.1.3 Neurological Features

Raised intracranial pressure and hydrocephalus due to craniosynostosis is often an associated feature, and skull radiographs show a significant increase in convolutional impressions (David et al., 1982) in affected individuals. Chronic tonsillar herniation and jugular foramen stenosis with venous obstruction have also been reported (Cinalli et al., 1995).

2.3.2 Apert syndrome

Described by Apert in 1906 (Apert, 1906), this syndrome is unique because of the syndactyly (fusions), of the digits of the hands and feet, which occur as a constant or frequent concomitant.

2.3.2.1 Prevalence

On the basis of pooled data from USA, Denmark, Italy and Spain (M.M.Cohen, et al., 1992), birth prevalence estimates of 15.5 in one million births have been made, accounting for 4-5% of all craniosynostosis cases (M.M. Cohen, & Kreiborg, 1992; Tolarová, Harris, Ordway, & Vagervik, 1997). David et al., (1982) reported an

incidence of 1 in 317,000 in his South Australian patient series seen between 1961 and 1975.

2.3.2.2 Clinical Features

Apert syndrome is characterised by distinct craniofacial malformations involving the skull and midface. Distinctive deformities of the fingers and toes usually make this condition distinguishable from other craniofacial syndromes. The head is turricephalic; appearing disproportionately high, wide and short from front to back. Most commonly, both coronal sutures are fused, thus limiting anterior-posterior cranial growth. Growth of the anterior cranium, and its contents, may be restricted by fusion of the metopic suture of the mid-forehead. Additional premature fusion of the squamosal and sagittal sutures may also occur. The anterior fontanelle, although frequently open at birth, varies in its rate of closure. Characteristic of Apert syndrome is the symmetric fusion of the fingers and sometimes, toes. This varies in degree of severity from incomplete webbing of two digits to complete joining of digits and nails. The webbed hands make independent movement of the fingers difficult and as a result, the child may have trouble performing fine motor tasks. In terms of the facial appearance, the eye sockets appear slightly wide-spaced, the eyeballs protrude and the eyelids slant downwards at the lateral segment. The upper jawbone is underdeveloped and nose and lower jaw relatively prominent. Ears may appear low-set relative to the facial proportions. A cleft plate is not uncommon (42% of the cases of Lajeunie et al., 1999), and associated speech difficulties occur with relative frequency. Additional skeletal and visceral abnormalities have also been reported in this condition. Conductive deafness and increased liability to otitis media resulting from abnormal upper airway anatomic abnormalities has been noted.

2.3.2.3 Neurological Features

The brain is overgrown (megelencephalic) (M.M.Cohen & Kreiborg, 1990) in the misshapen skull. Central nervous system abnormalities are seen more frequently in this, than other syndromic disorders (Renier et al., 1996), and include malformations of the corpus callosum, limbic structures, cerebral white matter and grey matter (M.M.Cohen & Kreiborg, 1993). The ventricles commonly appear enlarged and hydrocephalus is frequently present (Fishman, Hogan, & Dodge, 1971; Hogan & Bauman, 1971).

2.3.3 Saethre-Chotzen syndrome

2.3.3.1 Clinical Features

Described by Saethre in 1931 (Saethre, 1931) and Chotzen in 1932 (Chotzen, 1932), this syndrome is characterised by coronal synostosis, usually affecting one coronal suture, although there may be bicoronal involvement. Facial asymmetry is common. The frontal hairline is usually low; there is mild midface retrusion, wide-set eyes, 'droopy' eyelid/s and ear shape anomalies. The nose may be beaked. Some cases of mild soft tissue fusion in the hands or feet have been reported, as has cleft palate (Kreiborg, Pruzansky, & Pashayan, 1972). Mild conductive hearing loss occurs commonly (Ensink, Marres, Brunner, & Cremers, 1996).

2.3.3.2 Neurological Features

Saethre-Chotzen is infrequently associated with neurological anomalies, although neonatal seizures, epilepsy and brain lesions have been reported in patients seen by (Elia et al., 1996).

2.3.4 Pfeiffer syndrome

Described by Pfeiffer in 1964 (Pfeiffer, 1964), this syndrome is characterised by craniofacial abnormalities as well as hand and feet anomalies.

2.3.4.1 Clinical Features

M. M. Cohen (1993b) proposed three clinical subtypes of Pfeiffer syndrome, of which there may be clinical overlap.

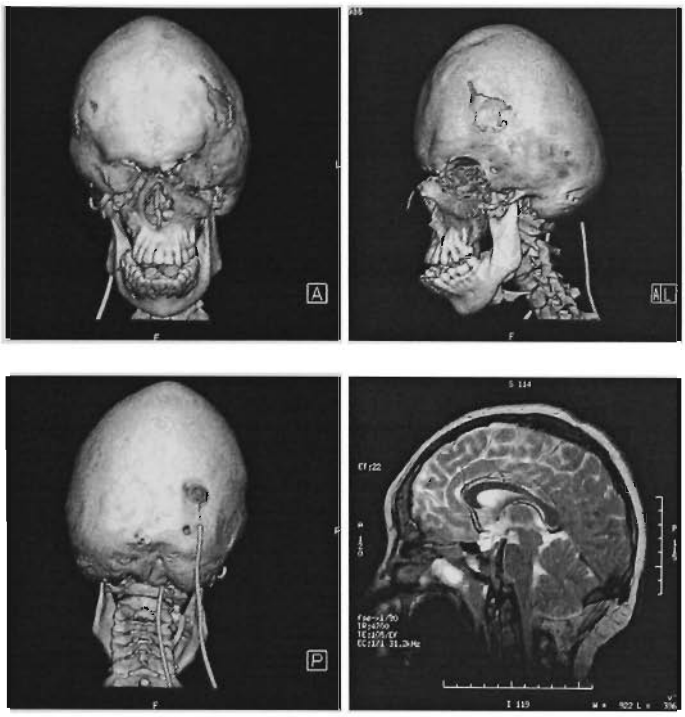
In classic (Type 1) Pfeiffer syndrome, there is bicoronal synostosis, and there may be additional involvement of the sagittal and metopic sutures. There is also midface retrusion, wide-set eyes and downslanting eyelids laterally. The thumbs and great toes are broad, and turned inward toward the midline. Type 2 Pfeiffer syndrome is characterised by a cloverleaf shaped skull, severe ocular proptosis, elbow abnormalities and broad thumbs and great toes (e.g. Kroczek, Muhlbauer, & Zimmermann, 1986; Plomp et al., 1998). Type 3 Pfeiffer syndrome is similar to type 2, but lacks the cloverleaf skull. Characteristics features of the condition include severe ocular proptosis, shallow orbits and marked shortness of the cranial base.

2.3.4.2 Neurological Features

Central nervous system involvement occurs with much higher frequency in type 2 and 3 Pfeiffer syndrome than the type 1 form (M. M. Cohen & MacLean, 2000). Commonly occurring anomalies include distortion ventriculomegaly, midline calvarial defect, progressive hydrocephalus and cerebellar herniation (Gorlin, M.M. Cohen, & Hennekam, 2001).

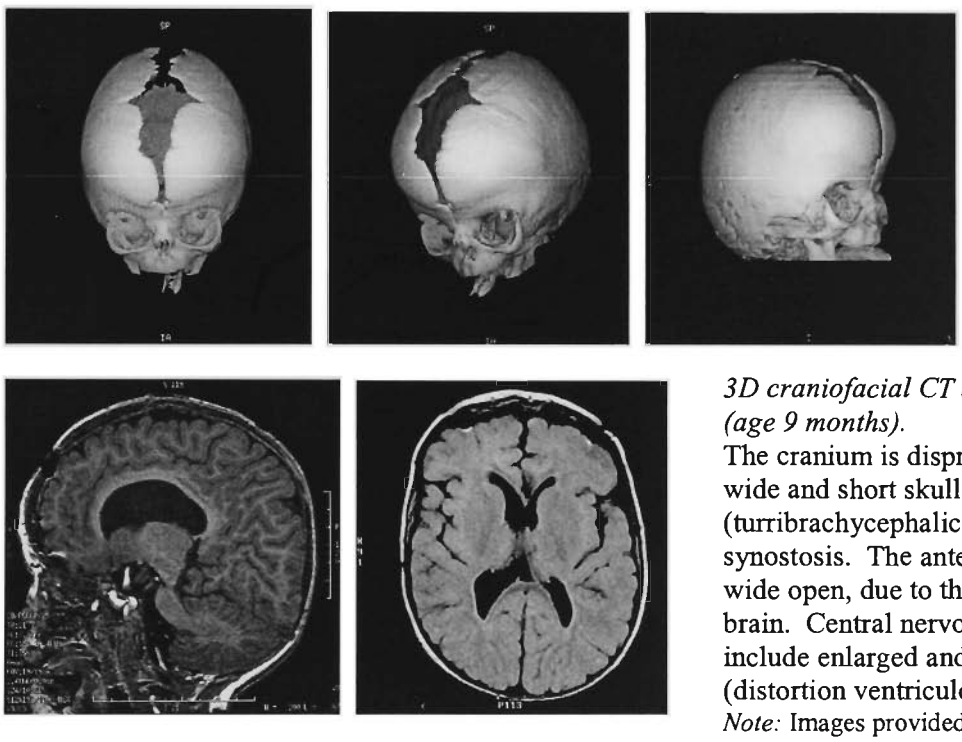
SYNDROMIC CRANIOSYNOSTOSES

Figure 2-1 Crouzon Syndrome: 3D craniofacial CT and MRI brain scans



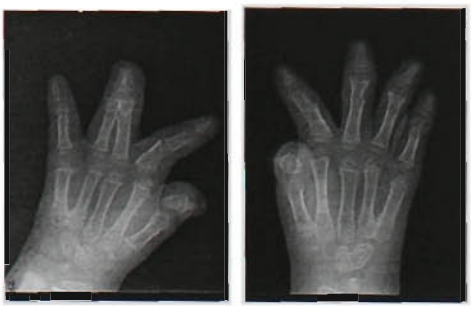
3D craniofacial CT scan (age 11 years).
Brachycephalic skull shape resulting from premature fusion of the sagittal suture and both coronal sutures. The calvaria is turricephalic; short, with a high steep forehead. Anteroposterior growth is restricted, with a shallow anterior and crowded posterior fossae.
MRI brain scan (age 14 years).
This shows prominence of the lateral ventricles, with no discernible fourth ventricle.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

Figure 2-2 Apert Syndrome: 3D Craniofacial CT and MRI brain scans



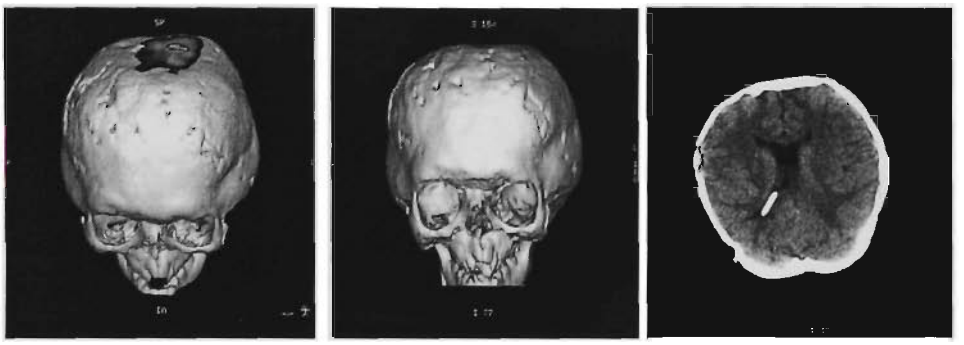
3D craniofacial CT and MRI brain scans (age 9 months).
The cranium is disproportionately high, wide and short skull from front to back (turribrachycephalic). There is bicoronal synostosis. The anterior fontanelles are wide open, due to the megelencephalic brain. Central nervous system anomalies include enlarged and distorted ventricles (distortion ventriculomegaly).
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

Figure 2-3 Apert Syndrome: Hand x-rays



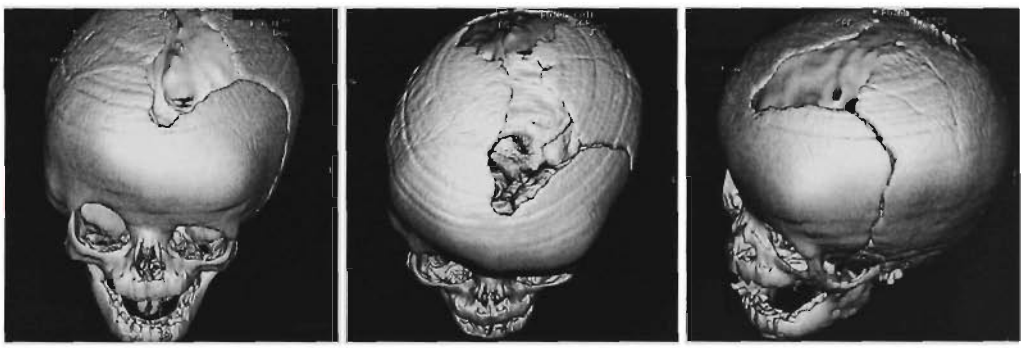
X-ray hands (age 3 years).
This shows syndactyly (fusion) of the fingers. Toes are also typically affected.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

Figure 2-4 Pfeiffer Syndrome; 3D craniofacial CT and MRI brain scans



3D craniofacial CT and MRI brain, age 7 years. The 'cloverleaf skull' is short from front to back and transversely wide. The frontal region is narrowed with prominent depression between the frontal bones and the temporal bones. MRI shows a ventricular peritoneal shunt in situ. There is increased prominence of the temporal horns of the lateral ventricles, and crowding of the structures of the posterior fossa.

Figure 2-5 Saethre-Chotzen Syndrome: 3D craniofacial CT scans



3D craniofacial CT scans (age 6 months)
There is right unicoronal synostosis. The right frontal bone is flattened and recessed, with bulging of the opposing left frontal bone and contralateral parietal bone. There is moderate bulging of the left temporal region laterally.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

2.4 The Nonsyndromic Craniosynostoses

The most commonly occurring craniosynostoses are the nonsyndromic types, with sagittal synostosis predominating, followed by coronal synostosis. Metopic and lambdoid synostosis occurs less frequently. In figures 2-6 to 2-8, three-dimensional computed tomography (CT) craniofacial imaging scans, x-ray and computed tomography magnetic resonance imaging (MRI) brain scans have been presented for the major nonsyndromic craniosynostoses discussed below.

2.4.1 Sagittal synostosis (Scaphocephaly)

2.4.1.1 Prevalence

The most common of the craniosynostoses, sagittal synostosis has been reported with an estimated birth prevalence of 190 in 1,000,000 births (Lajeunie, Merrer et al., 1995). In Australia, David and his colleagues David et al., (1982) reported that this disorder represented 47.2% of their patients with simple calvarial deformities; representing 35.1% of their entire South Australian craniosynostosis patient series. There appears to be a strong male preponderance (David et al., 1982; Shillito & Matson, 1968).

2.4.1.2 Clinical Features

Sagittal synostosis refers to partial or complete synostosis of the sagittal suture, which separates the right and left halves of the skull running longitudinally between the coronal suture anteriorly and the lambdoid suture posteriorly. It can be distinguished by an elongated, narrow 'boat shaped' head with prominence of the forehead and occiput (scaphocephaly). The anterior fontanelle is small and narrow, often closing early. The forehead is usually high and may be rather prominent.

2.4.2 Coronal synostosis (Plagiocephaly)

These common deformities are characterised by cranial and facial asymmetry. There are two main types; frontal plagiocephaly and occipital plagiocephaly and one, much rarer form; hemicranial plagiocephaly. The two main types of plagiocephaly have been included in the present study, and are described below.

2.4.3 Unicoronal synostosis (frontal plagiocephaly)

Coronal synostosis forms the largest group of plagiocephalic entities. The coronal suture separates the anterior cranial segment from the middle portion. On the affected side there is a concave basal skull curvature with orbital deformity and often synostosis of the sphenofrontal suture; the continuation of the coronal suture into the cranial base. The anterior fontanelle is sometimes small or asymmetrical. The anterior cranial fossae is especially short; the cranial base is extremely asymmetric, being much shorter on the affected side than on the unaffected side (David et al., 1982; Kreiborg, 1981). There is compensatory skull expansion in the anterior portion of the skull opposing the fused suture, as well as flattening in the occipital region contralateral to the fused sutural site.

2.4.3.1 Prevalence

Lajeunie, Le Merrer et al., (1995) estimated a birth prevalence of 94 in 1,000,000 livebirths. David et al., (1982) reported an incidence of unicoronal synostosis in 18.5% of his patients with simple calvarial deformities and 14.9% of all craniofacial syndromes. Contrastingly, this figure has been cited as 8.8% (F. Anderson & Geiger, 1965) in nearly all-inclusive samples of syndromic and nonsyndromic conditions. A female preponderance has been indicated by several authors (David et al., 1982; Montaut & Stricker, 1977; Shillito & Matson, 1968).

2.4.3.2 Clinical Features

Facial characteristics include a flattened and indented frontal region on the affected side, particularly laterally and frontal lobe volume is reduced on this side. The temporal bone on the same side may bulge laterally, and there is always some compensatory bulging of the opposing frontal and parietal bones. The orbit is set further back. The bridge of the nose deviates towards the side of the synostosis.

2.4.3.3 Neurological Features

David et al., (1982) reported no signs of raised intracranial pressure in the condition, but noted a localised increase in convolutional markings in the affected frontal bone in several cases, suggesting that brain growth here is more rapid than expansion of the cranial vault region. Foltz & Loeser (1975) noted a deformity of

the ipsilateral frontal ventricular horn in one case, and David et al., (1982) reported one case of mild ventricular dilatation in their series.

2.4.4 Lambdoid synostosis (Occipital plagiocephaly)

This extremely rare condition involves cranial growth delay in the lambdoid zone. True lambdoid synostosis can be distinguished from positional flattening (deformational plagiocephaly), which is a typically reversible deformity, which, like lambdoid synostosis results in posterior skull flattening, however there is no actual synostosis involved.

2.4.4.1 Prevalence

Incidence rates for occipital plagiocephaly are low, such as 1.3% (Matson, 1969). David et al., (1982) reported an incidence of 8.9% of calvarial deformities of their nonsyndromic South Australian series. The authors also indicated a male preponderance. The condition appears rarely associated with raised intracranial pressure or other anomalies, and hence incomplete ascertainment may be responsible for its apparent rarity.

2.4.4.2 Clinical Features

This condition is characterised by flattening of the occiput on the affected side, as well as advancement of the ear and prominence of the frontal region on the same side.

2.4.5 Bicoronal synostosis (brachycephaly)

Fusion of both coronal sutures has a heterogeneous etiology. It is the most commonly occurring craniosynostosis in the three main syndromic craniofacial disorders: Crouzon, Pfeiffer and Apert syndromes, and also occurs as a nonsyndromic entity. There may be additional involvement of minor frontal region sutures in this condition (Seeger & Gabrielsen, 1971). Anterior cranial fossae growth is severely limited in bicoronal synostosis, with compensatory skull growth in the middle fossae. Hence, the anterior extent of the temporal lobes may actually be in front of the frontal lobes.

2.4.5.1 Clinical Features

The skull shape is short from the front to the back of the skull and transversely wide. The forehead and occiput are flattened and the midface becomes progressively underdeveloped. The orbits are small and progressive bulging of the eyes frequently occurs.

2.4.6 Metopic craniosynostosis (Trigonocephaly)

There are two forms of the condition: a major group in which metopic synostosis occurs as an isolated malformation and a second group in which other primary defects of morphogenesis also occur (M. M. Cohen, 1986; Sargent, Burn, Baraitser, & Pembrey, 1985) or result from fetal head constraint (Graham et al., 1979).

2.4.6.1 Prevalence

Lajeunie et al., (1998) estimated a birth prevalence of metopic synostosis of 67 in 1,000,000; with a male: female ratio of 3.3:1. Incidence rates have ranged between 3.7% (Bertelsen, 1958) and 10.3% (F. Anderson & Geiger, 1965).

2.4.6.2 Clinical Features

Metopic sutural fusion results in a triangular, wedge-shaped appearance of the forehead. This frontal deformation is always associated with ocular hypotelorism; hence the eyes appear too close together. The forehead is narrow and temporal regions slope forward to merge with the frontal bones. There may be a mild convergent squint. The eyes take on an upward slant of the lateral end due to the cranial deformity.

2.4.6.3 Neurological Features

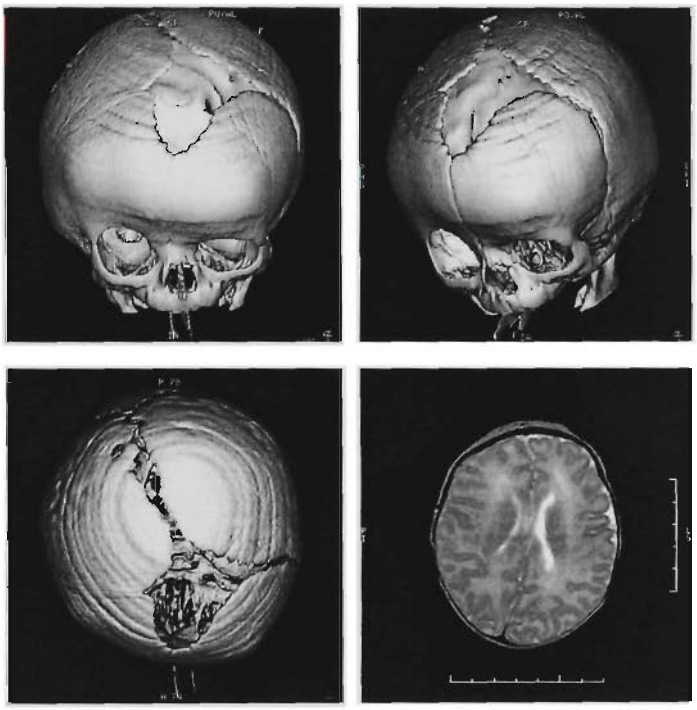
Shillito & Matson (1968) reported the presence of raised intracranial pressure in 19% of their patient series.

2.4.7 Multisutural synostosis and related conditions

This condition involving fusion of multiple sutures can produce various head shapes, depending on the sutures involved and the rate and order of sutural synostosis. In 'true' oxycephaly, which involves the coronal and sagittal sutures, the head appears pointed in shape, abnormally high and conical; the forehead recessed

and tilted backwards. The anterior base appears short. A form of turricephaly will result with primary involvement of the coronal suture, a form of scaphocephaly when the sagittal suture is initially involved. The cloverleaf skull abnormality occurs as a consequence of multiple sutural fusion; a constriction ring develops in the lambdoid-squamosal zone and allows some disproportionate bulging in the frontal and temporal bones. As the name suggests, the skull takes on a cloverleaf shape. Hydrocephalus occurs in the majority of cases of cloverleaf skull deformity.

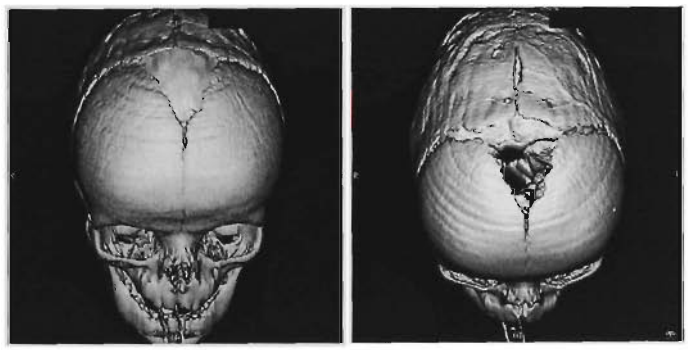
Figure 2-6 Unicoronal Synostosis: 3D craniofacial CT and MRI brain scans



3D craniofacial CT (age 4 months). Fusion of the right coronal suture (also affects left coronal suture) situated in the anterior skull portion. This produces asymmetric forehead flattening and recession on the affected side, and compensatory bulging in the opposing frontal and contralateral occipital regions.

MRI brain (age 3 days). This reveals moderately severe flattening of the right frontal region.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

Figure 2-7 Sagittal Synostosis: 3D Craniofacial CT and MRI brain scans



3D craniofacial CT (age 5 months). Fusion of the longitudinal sagittal suture stops growth laterally. It produces a narrow, elongated head shape due to compensatory growth in the anteroposterior direction. There is bulging of the frontal and occipital regions.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

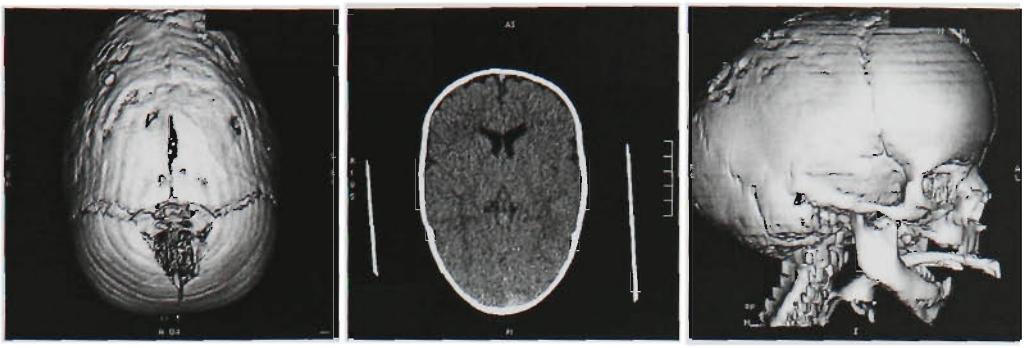
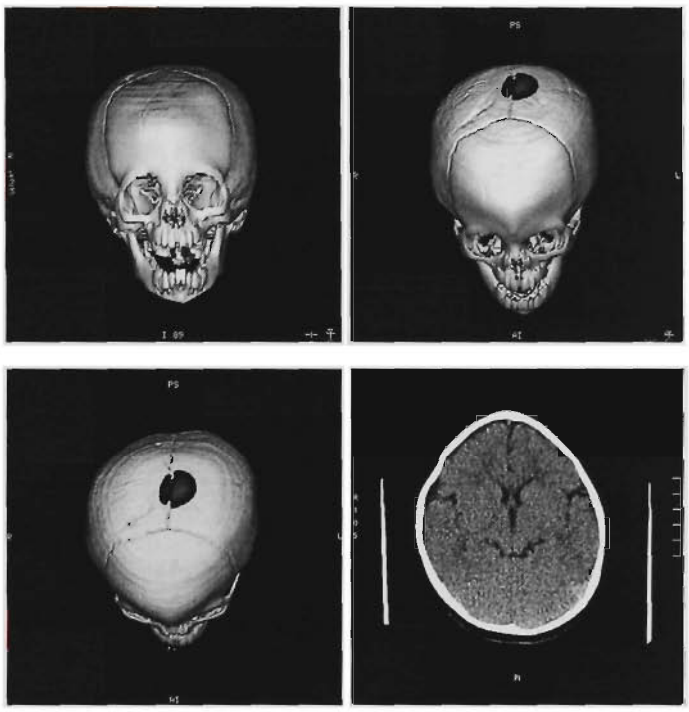


Figure 2-8 Metopic Synostosis: 3D Craniofacial CT and MRI brain scans



3D craniofacial CT (age 14 months). Fusion of the metopic suture separating the frontal bones produces a triangular appearance to the forehead and a shallow, narrow anterior cranial fossa.
MRI brain (age 4 weeks). This shows narrow and shallow anterior cranial fossa.
Note: Images provided courtesy of the Royal Children's Hospital. Printed with the author's permission.

Chapter Three

3 The Central Nervous System and Craniosynostosis

This chapter reviews the literature on normal central nervous system formation and maturation. The potential implications of the pathological mechanism of craniosynostosis upon the central nervous system and related cognitive processes are then addressed.

3.1 Cerebral Development

The central nervous system can be identified quite early in gestation. The main concept in central nervous system growth is that, like other developmental processes, it occurs along a continuum, proceeding from conception into adulthood following a sequence of precise, genetically determined stages (V. Anderson, Northam, Hendy, & Wrennall, 2001).

Most rapid brain growth occurs prenatally, when approximately 250,000 brain cells are formed through continuous rapid cell division (Papalia & Olds, 1992). This period of growth is primarily associated with formation of the structural units of the central nervous system (CNS), and is thought to be largely genetically determined. Postnatal brain growth mechanisms are largely associated with neural differentiation, maturation and elaboration of cortical circuitry in addition to biochemical changes. The mechanism of development of the CNS involves a gradual "fine-tuning" of the cerebral system, characterised by initial neural growth, and later, specification and ultimate connectivity within and between functional systems until optimal efficiency is achieved.

The timing of CNS maturation is thought to occur in a hierarchical fashion, with cerebellar and brain stem areas maturing first, followed by posterior and lastly anterior brain regions, particularly the frontal cortex (Fuster, 1993; Kolb & Fantie, 1989; Risser & Edgell, 1988). This process is accompanied by a series of growth spurts; the first of which has been documented to occur at 24-25 weeks gestation around the completion of neuronal generation, another during the first year of life, with later spurts between 7 and 9 years of age and lastly around 16-19 years of age (Hudspeth & Pribram, 1990; Klinberg, Viadya, Gabrieli, Moseley, & Hedehus,

1999). Intrinsic to the maturation of the CNS is the notion of critical or 'sensitive' periods. These represent 'windows of opportunity' which are important for the major progression and consolidation of key behavioural functions that are critical to the acquisition of subsequent skills, and the establishment of interconnectivity with other systems. The pre- and postnatal maturation of the CNS is thus a complex, interactional and interdependent process in which the timing and maturation of functional processes is dependent to some degree on preceding phases in the developmental course.

3.2 Mechanisms of Disruption to Normal Central Nervous System Development

Any interruptions during the tightly defined and sequentially organised process of CNS maturation may divert its expected developmental course. When occurring during the pre- and postnatal periods, potentially dramatic and irreversible changes to the outcome of the central nervous system can ensue. Prenatally, biological agents, such as genetic mechanism or intrauterine trauma (e.g. infections, injury) can result in significant abnormal structural brain morphology and cerebral reorganisation.

Postnatally, the immature brain has a higher susceptibility to environmental and experiential influences than within the prenatal period (Nowakowski, 1996). Risk factors for anomalous CNS development at this phase include birth complications, external trauma and cerebral infection. Postnatal injury typically has less impact upon brain morphology, instead interfering with the ongoing processes of CNS elaboration, including the development of the complex interconnections between functional units of the CNS which govern cognition.

Several authors have addressed the importance of critical periods for the final outcome of the CNS. Mogford & Bishop (1993), for example, contended that critical periods reflect "the time window during which external influences have a significant effect" (p.252). As noted above, critical periods occur within both the prenatal and postnatal periods as well as throughout early childhood and into late adolescence. Injury during these periods of heightened vulnerability may have particularly deleterious ramifications for the outcome of the CNS.

Psychosocial factors, such as the quality of the mother-child relationship, environmental stimulation and social support networks are also acknowledged for their impact on development. Poorer developmental outcomes in motor, cognitive and social-emotional functioning in infant studies have been related to deleterious psychosocial risk factors (e.g. Laucht, Esser, & Schmidt, 1997).

3.3 Recovery Mechanisms following Central Nervous System Injury

Conflicting theories have emerged about the recovery trajectory following early brain injury. A prevailing tenet has been that early onset brain injury is associated with a more favourable prognosis for long-term outcomes than comparable injuries acquired in adulthood. This notion has been derived largely from the principles of Margaret Kennard's (Kennard, 1938, 1942) early experimental studies of motor cortex lesions in infant and adult monkeys. Her work identified less severe consequences of similar motor cortex lesions in infant than adult monkeys; leading to the hypothesis that there was relative sparing of function following early cerebral insult such that the younger brain was more capable of transfer of functions from damaged to healthy cerebral tissue, which supported behavioural recovery in this group. On the basis of such findings, the "Kennard Principle" emerged, which espoused the notion that the immature brain is capable of considerable plasticity and functional reorganisation; hence "the earlier the brain damage the better the outcome".

Contemporary researchers have challenged the early Kennard-like principles around cerebral plasticity, contending instead that the true picture is more likely one of increased vulnerability for the underdeveloped brain (Finger & Stein, 1982; M. Johnson, 1997; Kolb & Gibb, 1999), with disruptions to rapidly developing neuronal networks, including subcortical and frontal regions, affecting the final outcome of the CNS (V. Anderson & Pentland, 1998). Anatomical evidence has shown that functional recovery following early cortical injury is correlated with a reorganisation of remaining cortical circuitry; the mechanisms of which vary with respect to timing (age) and nature (focal or generalised) of insult (V. Anderson, 1988; Kolb, Gibb, & Gorny, 2000; Mogford & Bishop, 1993; Woods, 1980). However, this cortical reorganisation may not necessarily result in a functionally efficient CNS system with minimal implications. Indeed, recent research

employing structural imaging techniques has shown that skills may be maintained ineffectually by damaged tissues following prenatal CNS injury, leading to developmental delay (Duchowny et al., 1996; Leventer et al., 1999). Even postnatally, where neuronal transfer has been indicated, "crowding" of skills can occur, leading to a generalised depression of neuropsychological functions (Aram, 1988; Mogford & Bishop, 1993; Woods, 1980). Serial CT scans of children sustaining traumatic brain injury have also detected cerebral atrophy over time (V. Anderson & Pentland, 1998; Kolb, 1995; Stein & Spettell, 1995). Hence early CNS insult may interrupt ongoing maturation in a variety of ways that is detrimental to immediate as well as long-term neurological and cognitive outcomes.

Experimental studies over the past 50 years in a variety of lab species, provide evidence to suggest that it is the precise developmental stage that predicts the functional outcome of early cortical injury (Kolb, 1995). Poor functional outcome has been associated with injury to the cortex after neurogenesis is complete, and during the period of continuing cell migration. Kolb and colleagues (Kolb et al., 2000) contended that for humans, the least favourable time for cortical injury is likely at the end of the first gestational period, perhaps including the first month or so of life, whereas the most favourable time is around 1-2 years of age. The extent of behavioural recovery is also influenced by age at assessment, sex and lesion size.

Although there may be some functional plasticity early in life, there is evidence to suggest that the time frame may be quite restricted, and not necessarily related to age in a linear manner. For example, children with prenatal lesions or those sustaining insults during the first year of life have been found to exhibit particularly severe impairment (V. Anderson, Bond et al., 1997; Duchowny, 1996). In terms of vulnerable brain areas, frontal lobe regions have been implicated as susceptible to cortical malformations, possibly due to the late development of this cerebral region (Leventer et al., 1999), and the associated vulnerability to teratogenic or genetic influences (V. Anderson, Bond et al., 1997).

In summary, the literature to date suggests that primary determinants of the outcomes of disruption to CNS development include the nature, timing and severity of the injury. Disruption to normal CNS development during the gestational phase is most likely to produce structural malformations, whilst brain insult occurring

from the postnatal phase throughout childhood is more likely to be of a generalised nature, impacting on the brain as a whole.

In terms of the implications of CNS insult for cognitive outcomes, Dennis (1989) on the basis of her work in language development, suggested that there may be a detour or deviation in the normal pattern of behaviour following early onset injury. Dennis further contended that when brain dysfunction occurs in the context of an emerging skill, the onset of that skill may be delayed and/ or the order of acquisition may be garbled or out of normal sequence. This may result in a shortfall or deficiency in the final level of skill competence. This is particularly problematic in the formative years, when few skills have been established.

Hebb (1949) also addressed the issue of disruption to CNS maturation during "sensitive" developmental periods. Hebb contended that damage or dysfunction to a cerebral region at a critical stage may result in irreversible damage to the cognitive skill/s subsumed by that region. Consequently, the acquisition of later developing cognitive functions, which are critically dependent on the integrity of particular cerebral structures at certain stages of development for optimal development, may also be affected.

There is a range of research that supports the thrust of Dennis' model, which implies that the full impact of childhood brain injury is not clear until cognitive skills are completely developed. Many studies note the greater impact of younger age at insult (V. Anderson, Bond et al., 1997; Ewing-Cobbs et al., 1997; Ewing-Cobbs, Miner, Fletcher, & Levin, 1989), and indicate a relative deterioration in age-related performance with respect to cognitive abilities (V. Anderson & Moore, 1995; V. Anderson, Morse et al., 1997; Taylor & Alden, 1997). V. Anderson et al., (2001) tracked language development in infants sustaining bacterial meningitis in comparison to a healthy control group. Basic expressive language skills in the post-meningitic sample were found to be initially delayed at twelve months of age. Subsequent reassessments of this group at five years of age and during early adolescence revealed changes in the pattern of language deficits with time, with developing skills emerging at a delayed rate. Others have similarly documented a pattern of increasing functional impairment with time since injury (V. Anderson & Moore, 1995; Rubinstein, Varni, & Katz, 1990; Wrightson, McGinn, & Gronwall, 1995).

3.4 Risk factors for Cognitive Dysfunction in Craniosynostosis

As the above suggests, CNS formation and maturation is a complex process, involving a range of intimately related and interdependent sequential developmental processes. The findings of previous studies of acquired and chronic conditions of early brain damage can be extrapolated to craniosynostosis, whereby anomalous CNS formation and maturation can result from a number of potential risk factors during the pre- and perinatal periods. Indeed, much of the concern over craniosynostosis and many of the controversies of the treatment of the condition, relate to the possible detrimental effects on the brain. Risk factors, occurring in isolation or in combination, may be postulated to have potentially deleterious sequelae for cognitive outcomes in these disorders.

3.4.1 Focal Skull Distortions

Craniosynostosis may impair the normal relation between cerebral growth and enlargement of the cerebral capsule; the skull may essentially be too small for the rapidly growing brain, thus restricting its optimal growth capacity. Focal restrictions in the site of the synostosed suture/s, as well as in areas of compensatory expansion, may alter and restrict brain growth patterns in the affected site. Indeed, MRI imaging studies have demonstrated blunting of the underlying cortex in patients with craniosynostosis (Renier, Sainte-Rose, Marchac, & Hirsch, 1982).

3.4.2 Timing of onset

Craniosynostosis typically occurs inutero. The 'interference' to the normal growth patterns of the CNS by this pathological process during gestation may have detrimental implications for the subsequent elaboration of the CNS postnatally. This may be evident in gross signs of cognitive dysfunction, or in more subtle ways over time.

3.4.3 Raised Intracranial Pressure

Raised intracranial pressure (ICP), that is an increase in normal brain pressure, carries with it well-demonstrated risks to cognitive outcomes, as shown in craniosynostosis and other clinical conditions. Elevated ICP in craniosynostosis

can arise from the growth of the brain in an inadequate cranial cavity (Gault, Renier, Marchac, & Jones, 1992; Kerwin Williams, Ellenbogen & Gruss, 1999) due to hydrocephalus, increases in the volume of the brain tissue itself or increased cerebral blood volume. Disorders of craniosynostosis also carry the risk of transient episodes of elevated ICP, which can be localised to a brain region proximal to the fused suture (Kerwin Williams, Ellenbogen & Gruss, 1999). Indeed, focal regions of pressure and ischaemia have been identified in cerebral blood flow studies (Jane, Edgarton, Fullerton et al., 1978) in patients with sagittal synostosis.

Studies using direct and prolonged recording of ICP have shown that syndromic and multisutural craniosynostoses carry the highest risk of raised ICP. Of 492 patient recordings, Renier and colleagues (Renier et al., 2000) reported the highest rates of raised ICP in Crouzon (62.5%) and Apert (45%) syndromes, multisutural (60%) and bicoronal (31.3%) synostoses.

However, monosutural synostosis is certainly not without such risks. In an earlier study, Renier and his co-workers (Renier et al., 1982) measured preoperative ICP using an epidural pressure transducer in 75 patients (age range 6 weeks to 15 years) with mixed craniosynostoses. Elevated ICP was found in 12.7% of coronal and 13.8% of scaphocephaly cases. The lowest risk of raised ICP appears to be in metopic (7.7%) and lambdoid synostosis, with the latter carrying the lowest, if any, level of risk.

The risk of elevated ICP is reported to increase with age. For example, Arnaud, Renier, & Marchac (1995) found abnormally high ICP occurred more frequently in older children (20%) than those less than one year of age (2%) with sagittal synostosis.

Hydrocephalus, the excessive accumulation of fluid dilating the cerebral ventricles can result in raised ICP, and has been reported in 4 to 10% of craniosynostosis cases, predominantly in the syndromic disorders (Collman, Sorenson, Krausz, & Muhling, 1988; Golabi, Edwards, & Ousterhout, 1987; Hoffman & Hendrick, 1979; Noetzel, Marsh, Palkes, & Gado, 1985). Progressive hydrocephalus found more frequently in Pfeiffer and Crouzon syndromes than in Apert syndrome (M. M. Cohen & MacLean, 2000; Moore & Hanieh, 1994). Although distortion ventriculomegaly, the distorted appearance of the ventricles into a shape resembling hydrocephalus, is common in Apert syndrome (M. M. Cohen, & Kreiborg, 1990;

Hanieh & David, 1993), the condition is not typically associated with clinical signs of increased ICP.

The true frequency, characteristics and significance of increased ICP for cognitive outcomes in the craniosynostoses is difficult to determine, as raised ICP is difficult to diagnose without formal measuring, such as with an extradural sensor. This is particularly the case for the single sutural conditions where elevations in intracranial pressure appear less often and may present without obvious clinical signs, as well as in borderline or temporarily elevated cases. Methodological limitations of previous studies include bias towards seemingly symptomatic patients, leading to possible over-reporting in some patient groups, and variation in interpretation of pressure recordings.

3.4.4 Intracranial Volume Changes

Craniosynostosis tends to restrict cranial volume; the earlier the synostosis occurs, the more dramatic the effect on subsequent cranial growth and development. Restriction is typically greater with synostosis of two or more sutures than a single suture, except for scaphocephaly and Apert syndrome, where head circumference may be large.

Sgouros, Hockley, Henry Goldin, & Wake (1999) measured intracranial volume change via computerized tomography (CT) scans in 84 patients with syndromic and nonsyndromic craniosynostosis prior to cranial expansion surgery and compared this data to a model of normal intracranial volume growth. Cranial volumes in eight patients were also measured postoperatively. Patients ranged between 1 and 39 months of age with 76% less than 12 months of age. Study findings showed little difference in intracranial volume change among the various craniosynostoses subtypes. Excluding children with complex multisutural synostosis, despite smaller intracranial volume at birth in individuals with craniosynostosis, intracranial volume had reached normal levels by the age of 6 months, and from that point on was found to follow the pattern of normal head growth. Their findings supported the notion of the maximum constricting effect of craniosynostosis occurring at birth, but gradually declining and becoming "burnt out" by the age of 6 to 9 months. Despite this reported normalization of intracranial volume over time, the small

postnatal intracranial volumes at birth may present long-term cognitive implications due to the rapid growth of the brain in this developmental phase.

3.4.5 Cerebral Structural Anomalies

Cerebral structural anomalies are associated with cognitive dysfunction, and occur most commonly in the syndromic craniosynostoses. Apert Syndrome is perhaps the most often associated with structural malformations, and is uniquely characterized by the megelencephalic (overly large) brain. Other anomalies identified in this condition include distortion ventriculomegaly (Hanieh & David, 1993; Renier et al., 1996), hypoplasia of the corpus callosum, agenesis of the corpus callosum and cavum septum pellucidum (Renier et al., 1996), chronic tonsillar herniation (Cinalli et al., 1995), gyral abnormalities (M. M. Cohen & Kreiborg, 1990; de Léon, de Léon, Grover, Zaeri, & Alburger, 1987), hippocampal abnormalities (M. M. Cohen, & Kreiborg, 1990; Crome, 1961; de Léon et al., 1987), pyramidal tract abnormalities (Maksem & Rossemann, 1979), frank encephalocele (M. M. Cohen & Kreiborg, 1990) and hypoplasia of the cerebral white matter and heterotopic grey matter (M. M. Cohen & Kreiborg, 1990). The megelencephalic brain in Apert syndrome which is found to arise from the time of cell proliferation (2-5 months gestation; V. Anderson et al., (2001), may be a contributory factor for the significant neurological correlates of this condition.

Quite significant CNS anomalies are commonly encountered in Pfeiffer syndrome, including ventriculomegaly (Tokumaru, Barkovich, Ciricillo, & Edwards, 1996), midline calvarial defect (Tokumaru et al., 1996) and cerebellar herniation (Kroczek et al., 1986; Tokumaru et al., 1996). Of the syndromic craniosynostoses, Saethre-Chotzen has been rarely associated with CNS malformations.

There is evidence to suggest that the brains of children with nonsyndromic craniosynostosis also differ morphologically from that of their nonafflicted peers. Bottero and colleagues (Bottero, Lajeunie, Arnaud, Marchac, & Renier, 1998) identified frontal subdural space distention and corpus callosum anomalies in their metopic synostosis patient series. Using MRI scanning technology, Marsh, Koby, & Lee (1993) identified abnormally small frontal lobes, excessive subarachnoid cerebrospinal fluid in the anterior fossae and widened precentral sulci in three consecutive patients with unoperated metopic synostosis. Aldridge et al., (2002)

examined children with nonsyndromic sagittal and metopic synostosis compared to non-affected children using 3-D magnetic resonance imaging (MRI). The authors reported substantial differences in the neural organisation of the brains of children with both forms of craniosynostosis, at both the cortical and subcortical levels, compared with children without craniosynostosis.

Epilepsy has been reported in the craniosynostoses, although the nature and rates of this condition has varied markedly among series. Infrequent occurrences of between 1% to 8% have been indicated in some patient series (David et al., 1982; Giuffré, Vagnozzi, & Savino, 1978; Montaut & Stricker, 1977).

3.4.6 Treatment

Treatment of craniosynostosis involves major reconstructive surgery, usually within the first year of life. This carries with it the inherent risks associated with any neurosurgical and craniofacial procedure, including intra-operative and postoperative complications. For example, fronto-orbital advancement is a technique used to expand and remodel the frontal façade of the cranium to accommodate the rapidly expanding brain and improve cosmetic appearance. A high incidence of frontal extradural collections following successful frontal advancement surgery has been identified in infants and young children with Apert syndrome (Moore & Abbott, 1996; Posnick, Lin, Jhawar, & Armstrong, 1994). Similarly, after successful correction of unilateral coronal synostosis, the previously "compressed" brain reportedly does not re-expand, but instead, cerebrospinal fluid occupies the newly created space (Moore & Hanieh, 1996).

An additional consideration is the timing of such intervention. It may be argued that manipulation of the cranium and its contents during a time of rapid brain growth and development can serve to disrupt CNS growth and elaboration processes, potentially causing a cessation of development or alteration in its normal course.

3.4.7 Other

Psychosocial factors are well acknowledged for their influence upon cognitive outcomes. Psychosocial research in the craniofacial disorders has found that the mothers of affected infants may be less socially responsive during the early part of

the first year than mothers of typical infants (Speltz, Goodell, Endriga, & Clarren, in press).

3.5 Summary and Conclusions

A number of hypotheses can be proposed about the potential contributory factors for cognitive dysfunction and nature of such deficits, in the craniosynostoses.

Firstly, biological factors such as genetic aberrations, may produce morphological differences in the brains of individuals with craniosynostosis. Secondly, cognitive dysfunction may arise from focal brain growth restrictions in the site of the synostosed suture/s as well as in areas of compensatory skull expansion. Thirdly, craniosynostosis carries with it the risks of raised intracranial pressure, the deleterious impact of which is well-recognised in this and other clinical conditions. The timing of onset of craniosynostosis, which typically occurs inutero, can potentially interefere with the structural formation and elaboration of the CNS. Surgical correction of craniosynostosis normally occurs within the first year of life, and hence during a vulnerable phase of CNS elaboration. Furthermore, this treatment intervention involves manipulation of the cranium and its contents, which carries with it the inherent risks of any neurosurgical and craniofacial procedure.

When cognitive dysfunction does accompany craniosynostosis, it is probable that a complex range of factors, acting alone or in combination, underlie the nature and severity of impairment. The individual contribution of these risk factors for cognitive dysfunction naturally varies, although is difficult to elucidate with accuracy.

One can draw on the early brain injury literature reviewed in this chapter in drawing inferences and predictions about the nature and timing of emergence of cognitive dysfunction that may manifest in the craniosynostoses. The literature reviewed presents contemporary evidence to suggest that brain injury acquired in the formative years is likely to have the effect of preventing, limiting and distorting the normal course of brain-behaviour relationships. With respect to the timing of emergence of cognitive deficits, due to the protracted course of CNS development, the impact of early damage may not be directly evident at a functional level until later in the maturational stage of development. In terms of the nature of cognitive dysfunction, those cognitive skills subsumed by frontal lobe systems, which mature

throughout childhood and adolescence, appear to be particularly vulnerable to early brain injury. Generalised disturbances of information processing (attention, memory, psychomotor skills) and executive functions, which are mediated by frontal brain regions, are more reported more frequently than focal deficits following early head injury (Dennis, 1989; Eslinger, Biddle, Pennington, & Page, 1999; Garth, V. Anderson, & Wrennall, 1997; Satz & Bullard-Bates, 1981) and thus anticipated in this population. More subtle interruptions may also affect developmental processes and schedules; these, however, may be more difficult to predict.

Chapter Four

4 The Neuropsychology of Craniosynostosis: Review of the Literature

The experimental literature which has addressed the cognitive and behavioural features of the syndromic and nonsyndromic craniosynostoses will be critically evaluated in this chapter.

4.1 Introduction

Most authors and clinicians involved in the multidisciplinary management of craniosynostosis will acknowledge a risk of cognitive impairment in all forms of the disorder. Some propose an increased risk of cognitive dysfunction that is directly related to the nature and number of affected sutures, this being highest in the multisutural conditions (e.g. Chumas, Cinalli, Arnaud, Marchac, & Renier, 1987). Others have contrastedly argued that there is no evidence for an increased risk of mental retardation based on a particular type of nonsyndromic craniosynostosis (Kapp-Simon, Figueroa, Jocher, & Schafer, 1993).

Numerous authors have attempted to elucidate the cognitive implications of craniosynostosis, at various time-points in the developmental trajectories of affected individuals, as well as determine whether differences exist in the cognitive profiles amongst the spectrum of craniofacial disorder subtypes. Several central themes have dominated the psychometric literature to date:

The neurodevelopmental characteristics of individuals with syndromic and nonsyndromic craniosynostosis have been investigated, with particular attention to the infant population. The developmental outcomes in the craniosynostoses have been studied, with respect to whether there is a decline in intellectual functioning over time. Some have also attempted to determine whether there exists an increased risk of learning and behavioural difficulties in these children as children mature.

The effect of cranial release and reconstruction surgery upon cognitive and psychomotor development can arguably be said to have dominated the psychometric literature on the craniosynostoses. This has involved comparisons of operated and unoperated patients on neurodevelopmental measures in an attempt to determine the functional implications of surgical versus nonsurgical management of

craniosynostosis. In a similar vein, the optimal time for cranial expansion surgery has been investigated by comparisons of early (<1 year of age) and late (> 1 year of age) operative synostosis patients on age-appropriate cognitive measures.

Predictors and correlates of cognitive outcomes have been examined in some studies, for example, examining psychometric data alongside neuroimaging, genetics, surgical, perinatal and psychosocial parameters.

The following literature review will address the above key areas that are pertinent to understanding the potential implications of craniosynostosis for cognitive growth and development.

4.2 Cognition in the Syndromic Craniosynostoses

4.2.1 Apert Syndrome

Apert Syndrome has historically been regarded as synonymous with intellectual disability. In their review of the literature, M. M. Cohen & Kreiborg (1990) stated that "...it is now reasonable to conclude that a significant proportion of Apert syndrome patients are mentally retarded". Such global generalisations have, however, been transcended by contemporary evidence that points to more variable intellectual profiles in Apert syndrome. Whilst the intelligence in individuals with Apert syndrome patients does appear to be skewed toward the lower end of the intellectual spectrum, many are of normal intelligence.

Renier et al., (1996) examined intelligence, and a range of other variables (age at operation, brain malformations, quality of the family environment) in 32 males and 28 females with Apert syndrome, whose mean age at first examination was 20 months (range 1 day-13 years). Intellectual assessments on 38 patients aged more than 3 years revealed a mean intellectual quotient (IQ) of 62 (range 10-114). Thirty two percent of these individuals were of at least normal intelligence (IQ>70).

Sarimski (1997) evaluated 11 German children aged between 2 years to 12 years who were recruited from a Parent Support Group. General cognitive abilities ranged from moderate mental retardation to normal intelligence (highest IQ score=101). Intellectual abilities were found to be normal (IQ>70) in 4 children;

borderline (IQ 70-79) in four and within the moderate range of mental retardation in three cases.

Lefebvre, Arndt, & Travis (1986) evaluated intelligence and psychosocial adjustment in 20 children with Apert syndrome who had undergone synostosis release in the first year of life, and ranged in age from 1 to 15 years. General intelligence and psychosocial functioning was evaluated at 6 months presurgery, and at 1, 2 and 4 years postsurgery. Whilst the mean age of patients at the time of testing was not specified and 5 children were unable to be formally assessed, the mean IQ of those examined was 73.6 (range 52-89); two children were of normal intelligence.

Shipster and colleagues (Shipster, Hearst, Dockrell, Kilby, & Hayward, 2003a) assessed cognition, speech and language abilities in a pilot study involving 10 children with Apert syndrome (age range 4 years 11 months to 5 years 11 months). Cognition was evaluated with the British Ability Scales. Six out of seven children assessed on the full test scored within the average range for general conceptual ability, and all achieved a nonverbal composite score within the average range. The authors concluded that IQ scores were considerably higher than that reported in previous studies. The difference between intellectual outcomes in this and previous studies of Apert syndrome may be attributable to a wide range of methodological factors, including the wide variation in ages tested between studies, and differences in the protocols and assessment measures employed.

In their review of the long-term natural history of patients with Apert syndrome, Patton, Goodship, Hayward, & Lansdown (1988) collected information on intelligence, education and employment history in 29 individuals who ranged in age from 8 to 35 years (mean 19.3 years). Formal and informal (where unable to administer standardised measures) evaluations of intellectual functioning were also conducted. Intellectual quotient scores of less than 100 were found in all subjects, suggesting a trend toward performances within the lower end of the intellectual spectrum: 48% (n=14) were of normal or borderline intelligence (IQ >70) whilst most (52%, n=15) performed within the intellectually disabled range.

4.2.2 Crouzon, Pfeiffer and Saethre-Chotzen syndromes

Whilst several published psychometric studies in Apert syndrome are available, methodologically sound empirical studies in the other syndromic conditions appear limited. The following literature review in Crouzon, Pfeiffer and Saethre-Chotzen syndromes hence largely comprises information obtained from anecdotal reports, very small patient series or individual case studies. The restricted sampling base, in part, reflects the rarity of these conditions.

In Crouzon syndrome, the incidence of intellectual disability is reported to be in the range of 0 to 20% (Andersson & Paranhos Gomes, 1968; Bertelsen, 1958; M. M. Cohen, 1979; Hunter & Rudd, 1977). In the few cases of Pfeiffer syndrome, most affected individuals appear to have normal intelligence (M. M. Cohen, 1979; Martsolf, Cracco, Carpenter, & O'Hara, 1971), although mild to moderate intellectual disability has been noted (M. M. Cohen, 1975; Saldino, Steinbach, & Epstein, 1972). Classic Pfeiffer syndrome (Type 1) is reported to be compatible with normal or near normal intelligence in most cases (Gorlin et al., 2001) with mild mental deficiency in others. Poorer cognitive outcomes have been expected to accompany the often-frequent central nervous system anomalies seen with Types II and III Pfeiffer syndrome.

Intelligence in Saethre-Chotzen syndrome is reported to be "usually normal", although a number of cases of mild-to-moderate mental deficiency have been documented (Bartsocas, Weber, & Crawford, 1970). More serious intellectual difficulties have been described in recent studies. In their 1996 paper, (Elia et al., 1996) reported that of eleven patients with Saethre-Chotzen syndrome (aged 6 to 28 years) undergoing psychometric evaluation, eight were reported to have intellectual disabilities, with four of these achieving IQ scores within the severe range of intellectual disability. Individuals with Saethre-Chotzen may present with TWIST gene mutations; significant learning difficulties have been identified in some individuals demonstrating specific microdeletions in neighbouring TWIST genes (D. Johnson et al., 1998).

The above studies highlight the wide variability that exists in intellectual functioning between, as well as within, the syndromic craniosynostoses. The interpretability and generalisability of some studies is however limited by the tendency to include individuals of wide age ranges in single samples, such as the

study of Patton et al., (1988), who reported on individuals with Apert syndrome aged between 8 and 35 years, which may conceal differences between younger and older individuals. As stated above, anecdotal reports and very small patient series are often reported on. The chief criticism of the majority of these studies is the quite limiting focus on the measuring global intellect alone in characterising these conditions. Despite the wide variability in level of functioning reported in the syndromic craniosynostoses, there appears to be no literature that has attempted to quantify the abilities of these individuals in more specific areas of cognition, such as attention, memory and learning skills and higher level 'executive' cognitive skills.

4.3 Cognition in the Nonsyndromic Craniosynostoses

Rates of intellectual disability in infant samples appear variable, but are generally lower than that of the syndromic conditions. Several studies have estimated the frequency of intellectual disability in sagittal synostosis to vary between 2.4% to as high as 66% (Andersson & Paranhos Gomes, 1968; Barritt, Brooksbank, & Simpson, 1981; Bertelsen, 1958; Hunter & Rudd, 1976; Ingraham, Alexander, & Matson, 1948; Shillito & Matson, 1968). In unicoronal synostosis, this has been estimated as between 2.6 to 10% (Hunter & Rudd, 1977; Shillito & Matson, 1968). Mental retardation appears more frequently in bicoronal synostosis, with an incidence of 3.5% to 26% reported (Brambilla, Pezotta, & Rognone, 1981; Feingold, O'Conner, Berkman, & Darling, 1969).

The mental development of infants and children with nonsyndromic craniosynostosis (i.e. craniosynostosis occurring in isolation from other abnormalities) has been the subject of particular controversy among treating professionals, with this age group comprising the focus of much of the developmental literature in the craniosynostoses. Unresolved issues centre on whether mental development differs from that of the normative population, whether there is deterioration in cognitive functioning in the absence or delay of craniofacial surgery, and also whether cranial expansion surgery actually minimizes the risk of cognitive dysfunction in affected individuals. Such issues have dominated the contemporary research involved in elucidating the functional repercussions of craniosynostosis and its related treatment upon cognition (e.g. Arnaud et al., 2002;

Arnaud et al., 1995; Kapp-Simon, 1998; Kapp-Simon et al., 1993; Speltz, Endriga, & Mouradian, 1997).

Numerous studies have reported that the cognitive development of infants with nonsyndromic craniosynostosis does not differ from the normative population during the infancy years in samples of mixed monosutural and multisutural synostosis (Kapp-Simon et al., (1993) and sagittal synostosis (Arnaud et al., 1995; Speltz et al., 1997).

Kapp-Simon et al., (1993) evaluated mental development in infants with nonsyndromic monosutural and multisutural craniosynostosis. Forty five (29 operated, 16 unoperated) infants aged between 2 to 33 months at recruitment were assessed on the mental development index (MDI) of the Bayley Scales of Infant Development (BSID). Twenty five of these subjects (19 operated, 6 unoperated) were reassessed on this measure approximately one year following initial evaluation. Kapp-Simon et al., (1993) reported that the initial evaluations yielded a range of mental development scores that approximated a normal distribution for the entire sample. Longitudinal analyses showed no significant differences in MDI scores between initial and follow-up evaluations for operated and unoperated subjects, and there were no interactions between surgery and time. These findings suggest that infants with nonsyndromic craniosynostosis display mental abilities consistent with normative population estimates during infancy, and that the mental developmental outcomes of surgically and nonsurgically managed infants does not differ over time, at least within the infant developmental phase.

Speltz et al., (1997) provided longitudinal developmental data on 19 infants with sagittal synostosis (surgically corrected at less than 8.5 months of age) and a demographically matched normal control group. Subjects were assessed at ages 4, 12 and 24 months on the Bayley Scales of Infant Development. Mental Development Index scores fell within the normal range in the craniosynostosis sample at each assessment, suggesting that mental development in infants with sagittal synostosis remains relatively stable, and within normative expectations, within the first two years of life.

Arnaud and colleagues (Arnaud et al., 1995) reported on a French sample of 396 patients with scaphocephaly treated at their craniofacial unit. One hundred (41 nonsurgical, 59 surgical) underwent preliminary psychometric assessments. The

mean age at preliminary consultation was 9 months and both patient groups were reviewed at approximately 6 years of age. Developmental assessments at the initial consultation yielded a range of scores representative of a normal distribution of intelligence in both the surgical and nonsurgical groups.

The above-reported studies which demonstrate that the mental development of infants with nonsyndromic craniosynostosis parallels a normal distribution during infancy, contrast with a small number of studies that have reported developmental delays in affected populations. Panchal et al., (2001) studied infants with mixed craniosynostosis (sagittal, metopic, unicoronal and bicoronal) and deformational plagiocephaly. Deformational plagiocephaly is a skull deformity involving flattening of the calvarium, usually in the occipital region, that resembles the skull shape anomaly of craniosynostosis. This condition differs from craniosynostosis in that there is no craniosynostosis in the affected skull area, and it is also a typically reversible condition. Panchal et al., (2001) reported psychomotor delays in preoperative infants with mixed craniosynostosis (sagittal, metopic, unicoronal and bicoronal).

Although the above research into the developmental functioning of infants with craniosynostosis may lend support to the contentions of several authors that craniosynostosis does not have clinically significant functional cognitive sequelae during the infancy years, a number of methodological and theoretical issues should however be considered prior to drawing inferences on the basis of these findings.

From a methodological perspective, one would optimally want to compare those children who underwent corrective surgery for craniosynostosis with those that did not, and for such individuals to be matched with respect to anatomic severity of the craniosynostosis. Arguably, the majority of cases not undergoing surgery that may have comprised comparison groups represent milder forms of craniosynostosis that may not be of sufficient severity to impact upon normal brain growth and development. One study by Kapp-Simon et al., (1993) which did address this issue found no correlation between anatomic severity and mental development in an infant sample.

In interpreting the significance of infancy study findings one must also consider the predictive limitations and integrity of the available infancy-based assessment tools for measuring global cognitive functioning. The majority of studies have utilised

the Bayley Scales of Infant Development- 2nd Edition (BSID-II) and its predecessor, the BSID. This assessment tool is weighted toward sensory-motor function and whilst it does accurately identify children who are likely to be retarded at age seven years, it does not reliably predict specific intelligence scores for children in the normal range (Sattler, 1990). Hence, the ability to draw predictive inferences about long-term intellectual outcomes on the basis of infancy-based assessments in normally functioning infants, and those with minimal brain dysfunction, is restricted.

Furthermore, summary scores provided by most infant tests may conceal differences in more specific areas of functioning, particularly within the late infancy years when there is a variable emergence and specialization of language and motor skills.

Cognitive functioning encompasses a wide range of abilities in different domains, including language, visual-spatial, attention, memory and executive skills, of which mature and become increasingly specialised at different rates over the course of an individual's development. Due to the protracted course of central nervous system development, the cognitive structure of infants is not sufficiently differentiated for detailed assessment of this wide range of abilities until near preschool age. It is plausible that the effect of craniosynostosis on cognition may hence be clinically meaningful only, or primarily over time, as these skills mature. This may be particularly so with respect to frontal lobe systems skills, which continue to develop up to the second decade of life, and are known to be vulnerable to the effects of early disruption to central nervous system development (Duchowny et al., 1996; Leventer et al., 1999).

It might also be contended that the nature and extent of cortical impairment might not be severe enough to result in global developmental delays but instead be focal, resulting in minor developmental delays and specific cognitive deficits. Whether subtle cognitive dysfunction; a sign of minimal brain dysfunction, will be detectable by the assessment of global mental and psychomotor functioning during infancy is questionable. The identification presence of minor cognitive deficits and learning difficulties and can only really be adequately assessed when a child reaches an age in which more in-depth and specialised neuropsychological measures, that provide greater precision and reliability, can be administered.

The literature on developmental outcomes in operated and unoperated samples of children and adolescents with nonsyndromic craniosynostosis may help elucidate some of the above dilemmas.

4.4 Developmental Outcomes in the Craniosynostoses

There is continuing debate as to whether intellectual functioning remains stable over time in the craniosynostoses, and/ or whether deficits in more specific cognitive domains emerge as children mature.

Several authors have addressed the developmental implications of craniosynostosis as this relates to intellectual factors, by examining the cognitive profiles of affected individuals as they mature. Some have found that intellectual functioning continues to remain within normal limits over time in the nonsyndromic craniosynostoses. For example, Arnaud et al., (1995) conducted review assessments of a French sample of 100 (41 nonsurgical, 59 surgical) patients with scaphocephaly (study described previously). When seen at approximately 6 years of age, both surgical and nonsurgical patients were found to continue to display intelligence scores paralleling the normal population distribution.

The findings of Arnaud et al., (1995), however, occur in the context of evaluation of global intellect only. When a more comprehensive sampling of the wide array of cognitive processes is undertaken, the majority of studies point to at least mild neurological and associated cognitive dysfunction in these children as they mature. Skills such as information processing, attention, and higher-level "executive" cognitive processes appear to be affected, and often manifest in the form of learning disorders and social and behavioural dysfunction (e.g. Bottero et al., 1998; Kapp-Simon, 1998; Magge, Westerfeld, Pruzinsky, & Persing, 2002; Rozelle, Marty-Grames, & Marsh, 1995; Sidoti, Marsh, Marty-Grames, & Noetzel, 1996).

In a sample of surgically treated children with sagittal synostosis aged 6 to 16 years (mean age 10.3 years), Magge et al., (2002) reported that, despite demonstrating a mean intellectual quotient within the normal range (and at a high average standard on the measure used; mean IQ=110.6), 50% of their sample displayed reading and/ or spelling learning disabilities. This is significantly higher than general population rates of 2%-10% (American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., 1994).

Despite the findings of normal developmental functioning during the infancy years, Kapp-Simon et al., (1993) did not preclude the possibility of specific learning disabilities in children with nonsyndromic craniosynostosis as they mature. Such notions were confirmed by the latter longitudinal study of Kapp-Simon (1998) in which mental development was evaluated across three time periods in children with nonsyndromic metopic, sagittal and unicoronal synostosis (mean age 8 months [TI], 21 months [T2] and 50 months [T3]). Whilst base rates of mental retardation were found to be consistent with normative population rates at T1 (1.4%), the incidence of retardation increased was reported to be two to three times normative expectations as children matured (6.5% at T2 and T3). Furthermore, learning disorders were indicated (on the basis of school and clinical records) in 47% of individuals for whom this information was available. Difficulties reported included reading and arithmetic disabilities, fine-motor/ visual-perceptual problems, Attention Deficit Hyperactivity Disorder (ADHD) and multiple disorders. Whilst these results should be interpreted conservatively, due to the use of non-standardised measures to diagnose learning difficulties (school/ clinical reports), these findings importantly suggest that the long-term developmental outcomes in the craniosynostosis are not without functional significance, and furthermore, that such deficits can emerge within the context of seemingly normal infant development.

Sidoti et al., (1996) retrospectively evaluated 32 individuals with metopic synostosis, 15 of whom were nonsurgically managed due to the mild nature of their condition. Longitudinal data was gathered on the basis of retrospective clinical information and researcher-constructed parental current developmental/ behavioural questionnaire. Patients ranged between 6 months and 22 years of age (mean 7 years 2 months) at the latest evaluation. Whilst 62% were deemed to show no cognitive or behavioural abnormalities, a wide range of mild neurological disabilities, including delayed speech and language, ADHD and learning disabilities were indicated in 38% of their sample. Subjects were divided into two age groups: less than 5 years of age (47.2%) and greater than 5 years of age (57.2%). A higher incidence of cognitive and behavioural difficulties was reported in children aged over 5 years (47.4%) compared with the younger group (17.6%), although differences may reflect the increased likelihood of detecting such difficulties as children mature. A higher frequency of developmental, speech and language

problems was reported in the operated group compared to the unoperated group was found, although this difference was not statistically significant and the sample size of the latter was small. The methodological limitations, which include the use of non-standardised evaluative criteria for cognitive and behavioural dysfunction, namely chart records and parental questionnaires (e.g. Does the patient have a behavioural problem?) limit the interpretability of these findings.

Bottero and colleagues (Bottero et al., 1998) conducted a longitudinal study of 76 children (mean age 6.5 years) with surgically corrected metopic synostosis. Children were evaluated prior to cranial surgery and again postoperatively at 3 months, 1 year and every 2-3 years thereafter. When seen at approximately 6.5 years of age, 68% of children reportedly showed no developmental problems, 26% displayed a specific developmental problem but satisfactory social functioning, and 5% showed major delay. Fourteen percent of the sample showed behavioural disturbances and problems with speech, reading and/or writing were also reported. The study findings were, however limited by the exclusion of mild trigonocephaly cases, unoperated cases (n=76), a criterion of IQ greater than 90 to represent normal intelligence and cases with insufficient follow-ups (n=66).

Lajeunie and colleagues (1998) compared the psychological functioning of 167 patients (mean age 4.8 years; range 6 months to 16.5 years) with syndromic and nonsyndromic metopic craniosynostosis. Their sample was divided into three groups; Group 1 (n=127) had nonsyndromal metopic synostosis; Group 2A (n=32) had craniosynostosis and one or more other malformations (e.g. visceral, limb, brain malformations); Group 2B (n=8) had craniosynostosis and accompanying chromosomal abnormalities. Patients with metopic synostosis in the presence of no other anomalies were reported to be functioning within the normal range (mean IQ of 103). However, below average performances were identified in those individuals in whom the craniosynostosis was accompanied by other malformations. These findings suggest an increased risk of intellectual difficulties in children with metopic synostosis in the context of accompanying chromosomal and/ or congenital malformations, compared with those with nonsyndromic metopic craniosynostosis.

Aberrant speech and language are often expected to accompany the craniosynostosis syndromes. Shipster, Hearst, Dockrell et al., (2003a) reported that eight of ten children with Apert syndrome who were assessed had moderate or severe language difficulties, with expressive language difficulties the most

frequently occurring. Language impairments may be attributable to a variety of factors. These include hearing impairments, clefts and other deformities of the maxilla and mandible which directly affect the vocal apparatus.

Whilst speech and language have not been identified with relative frequency in the nonsyndromic craniosynostoses, this in part, may reflect the lack of studies that have investigated this issue. There is, however, good empirical evidence (Rozelle et al., 1995; Shipster, Hearst, Somerville et al., 2003b) for an increased risk of speech-language disorders in school-aged children with sagittal synostosis. Shipster and colleagues (2003b) reported an increased incidence of speech and language impairments in the context of normal intelligence in 76 children with isolated sagittal synostosis, aged 9 months to 15 years. Whilst intellectual capabilities in this group closely paralleled the normal population distribution, 37% of children displayed speech and/ or language (receptive or expressive) impairment; twenty of whom met diagnostic criteria for moderate to severe specific speech and/ or language impairments. Six of thirteen children assessed fulfilled the criteria for literacy impairment. The speech/ language impairments could be accounted for by global cognitive impairments in only two of the 28 children. No association was found between identified impairments and peri-neonatal risk factors, history of otitis media, raised intracranial pressure nor operated/ unoperated status. A trend for children who had surgery over the age of 4 years to be 4 times more likely to have difficulties than children operated on at less than 6 months of age was found.

In another investigation into the speech and language characteristics of children with sagittal synostosis, Rozelle et al., (1995) reported significant impairments in language, phonology, articulation or any combination of the three in 29% of 38 children surgically treated for this condition.

As these studies suggest, minor or more severe learning difficulties have been detected in children with a variety of nonsyndromic craniosynostoses as these children mature. These findings occur in the context of longitudinal and cross-sectional data suggesting seemingly normal cognitive functioning during the infancy years.

4.5 Surgical Issues

The traditional treatment of craniosynostosis has been surgery to release the restriction on the growing skull, and in turn, enhance normal brain and skull growth (McLaurin, Schut, Venes, & Epstein, 1989).

Disagreement as to the objectives and potential outcomes of operative interventions in the management of craniosynostosis has continued by those involved in the multidisciplinary care of affected individuals. When several sutures are involved, there is a consensus view that the constricting effects of this condition carry the risk of elevation of intracranial pressure, thus necessitating surgical intervention.

The effect on the brain of single suture closure is, however, an issue of common dissent. The empirical literature on the topic of cranial vault surgery in single-suture cases has addressed whether surgical release of craniosynostosis is warranted solely on the basis of cosmetic grounds, or whether there may be additional concerns about the risks to cognitive development in these conditions. Some clinicians argue that the single-suture craniosynostoses are rarely complicated by intellectual or neurological dysfunction, and describe the absence of sequelae when nonsurgical care is provided (F. Anderson & Geiger, 1965; Barritt et al., 1981; Freeman & Borkowf, 1962; Hemple, Harris, Svien, & Holman, 1961; Hunter & Rudd, 1976). Others have pointed to deleterious cognitive outcomes in unoperated and late operated cases, and cite a combination of cosmetic and neuropsychological factors as pertinent to the decision to operate (Ingraham et al., 1948; Kaiser, 1988; McLaurin et al., 1989; Renier, Brunet, & Marchac, 1987; Shillito & Matson, 1968).

Multiple experimental studies in the psychological literature have compared the mental development of operated and unoperated infants in order to elucidate the functional cognitive significance of surgical intervention in craniosynostosis. Two main issues have been addressed: Firstly, does mental development of unoperated and unoperated infants differ and secondly, when is the right times to operate- are there functional implications of early (<12 months) versus late (> 12 months) cranial expansion surgery.

Conflicting findings have emerged from the literature to date.

4.5.1 Operative and non-operative comparisons

Infant studies comparing operative patients with nonsyndromic craniosynostosis against nonsurgically managed patients or normative population data, have reported no significant difference between the mental development of surgically and nonsurgically treated patients in infant samples of mixed synostosis (e.g. Kapp-Simon et al., 1993) and sagittal synostosis (e.g. Arnaud et al., 1995). On the basis of such findings, (Kapp-Simon et al., 1993) maintained that the indications for craniofacial surgery in children with simple synostosis are primarily cosmetic rather than functional, and that while the shape of the brain may be distorted in affected individuals, its functional capacity remains intact.

Several authors have challenged such contentions, however. Renier & Marchac, (1993) criticized the conclusions of Kapp-Simon and colleagues (Kapp-Simon et al., 1993), asserting that whilst extremely young children with craniosynostosis usually had normal mental development, this proportion decreased with age, especially when more than one suture was involved. Renier et al., (2000) conducted 979 assessments in their patient series of mixed syndromic and nonsyndromic craniosynostoses seen over a 23 year period. They found a significantly higher percentage of children with normal mental levels seen preoperatively before one year of age in comparison to those assessed after that time in all types of craniosynostoses, except for trigonocephaly, where comparable proportions were reported.

Sidoti et al., (1996) also reported a slightly higher, though nonsignificant presence of developmental, speech and language problems in operated than unoperated children with metopic synostosis.

Renier and Marchac (1993) posited another explanation for the cognitive differences between operative and non-operative samples of craniosynostosis patients. They contended that early corrective surgery stopped a regression in cognitive skills, and yielded better outcomes for the child than later surgery. Their views are consistent with those of multiple authors who contend a possible deterioration of mental function if surgery is not performed (Ingraham et al., 1948; Kaiser, 1988; McLaurin et al., 1989; Renier et al., 1987; Shillito & Matson, 1968).

4.5.2 Age at surgery and cognitive outcomes

Studies that have examined age at surgery as an outcome factor in the nonsyndromic craniosynostoses have yielded mixed findings. No differences in cognitive outcomes between early and late operative samples have been reported in infant (KA Kapp-Simon et al., 1993) and childhood samples (Kapp-Simon, 1998; Magge et al., 2002).

Kapp-Simon and colleagues (1993) reported no interactions between age at surgery and time in their sample of mixed nonsyndromic infants.

In her longitudinal study, Kapp-Simon (1998) found that learning disorders were as likely to be present in those with early correction of the synostosis as in those whose deformity was corrected at a later age or not corrected at all. Magge et al., (2002) reported no significant differences in the prevalence of learning disorders of early and late-operative children with sagittal synostosis. Such findings lend support the contentions of authors (e.g. Arnaud et al., 1995) that early surgical correction of single suture craniosynostosis hence neither prevents learning disabilities, nor improves cognitive functioning at a later age.

However, a number of studies have reported differences between samples of early and late- operative with craniosynostosis in infancy and longitudinal studies.

Shipster et al., (2003b) found a trend for increased age at operation to be associated with the presence of speech and language and/ or cognitive impairment in children with isolated sagittal synostosis (aged 9 months to 15 years). Children who had surgery over the age of 4 years were four times more likely to have such difficulties than children operated on at less than 6 months of age. Arnaud et al., (1995) compared presurgical developmental scores of a subtest of sagittal synostosis cases who had surgical excision of their synostosis before one year of age, with developmental scores of cases aged over one year at surgery. Whilst both groups were performing within the normal range of intelligence, those aged less than 1 year at the time of surgery were more likely to achieve mean mental development scores above 90. Whilst the authors interpreted these findings as indicating that the mental functioning of those with sagittal synostosis operated on later than one year of age was worse than that of those operated before that time, this tentative conclusion was based on cross-sectional data. Furthermore, age differences found may have been

specific to the standard score used to distinguish presumably 'delayed' and 'normal' infants (IQ ≥90) as opposed to the currently accepted criteria of an IQ of less than 70 (2 standard deviations below the population mean) to define clinically significant levels of mental deficiency.

Whilst statistically nonsignificant, Speltz et al., (1997) did find a negative correlation/ trend between age at surgery and mental development scores in his sagittal synostosis sample followed between 4 and 24 months of age.

Arnaud et al., (2002) reported better postoperative mental outcomes in infants with sagittal synostosis whose surgery was performed less than 1 year of age than after one year. Similarly, Bottero et al., (1998) reported better cognitive outcomes in metopic synostosis children undergoing cranial expansion at less than 1 year of age in comparison to those operated after that time, although other factors, such as severity of frontal stenosis and presence of extracranial malformations were also found to influence mental outcomes. Renier and colleagues (Renier et al., 2000) similarly found that children with all forms of nonsyndromic and syndromic craniosynostosis (except trigonocephaly) have better cognitive outcomes than those operated after that time.

Of the syndromic craniosynostoses, Renier et al., (1996) compared the intellectual functioning of 53 operative patients, of whom 37 (70%) had cranial release surgery before one year of age. Age at operation was identified as the main factor associated with changes in mental development in Apert syndrome children; IQ was greater than 70 in 50% of his sample operated on before 1 year of age versus only 7.1% of those operated on later in life. In contrast, Renier & Marchac (1988), in an earlier study, and Sarimski (1997) found no simple relationships between intellectual abilities and time of cranial surgery in their samples of Apert syndrome children. Renier & Marchac (1988) reported that the mental development appeared severely impaired regardless of how early the operation was performed.

In a sample of 171 children with mixed craniosynostosis Renier & Marchac (1988), 99% of 113 children operated on up to 1 year of age (n=113) reportedly had normal intellectual quotients, compared to 76% of 58 children operated on when aged 1 year.

In their study of 2137 cases of mixed craniosynostoses (syndromic and nonsyndromic) seen between 1976 and 1999, Renier et al., (2000) reported on 979 cases who underwent mental assessments, and who were operated on before or after 1 year of age. Children operated on before one year of age had significantly better mental outcomes than those operated after age one year. Whilst these findings indicated that percentages of patients with normal mental development ranged between 88-91% in single-suture synostosis these proportions were more variable in multisutural (brachycephaly, 9%) and syndromic (17%-81%) conditions.

Apparent from the combined findings of these studies is that there may be an increased risk for significant cognitive delay for a subgroup of children with single suture craniosynostosis. It is however difficult to conclude with certainty that surgery minimises or diminishes the risk of cognitive dysfunction in simple craniosynostosis based on the findings presented here. Furthermore, conclusions about the timing of surgery need to be interpreted with caution; severity of craniosynostosis is seldom controlled for in studies comparing early and late operative outcomes and may contribute to intellectual performance outcomes. It may be more plausible to conclude that early surgical intervention may not actually improve a child's mental status, since damage to the brain cannot be wholly reversed, but rather prevent a deterioration over time.

It is also important to address the timing of craniosynostosis. Since craniosynostosis typically manifests inutero, it may be that central nervous system damage occurs prenatally, thus early surgical repair of craniosynostosis postnatally may not prevent developmental delay, nor other cognitive deficits. The cognitive impairment observed in craniosynostosis may alternatively be simply related to currently unknown adverse effects of the condition upon cortical development. A wide range of other factors have been examined for their potential contribution to the presence and severity of cognitive dysfunction in the craniosynostoses, and are described below.

4.6 Predictors and Correlates of Cognitive Outcomes

A range of adverse risk factors have been addressed in the literature for their potential contribution to cognitive dysfunction in the craniosynostoses. These include raised intracranial pressure, primary abnormalities of neuronal

development, structural anomalies, brain damage associated with defective skull growth and shape, chromosomal abnormalities and syndromes. Other factors, such as the quality of social/ family environment also appear to be of importance.

4.6.1 Genetic, chromosomal and associated findings

As stated previously, significant learning difficulties have been identified in a small sample of individuals with Saethre-Chotzen who carry specific microdeletions of the TWIST gene (D. Johnson et al., 1998).

Whilst limited studies addressing genetic factors and cognitive outcomes in the nonsyndromic craniosynostosis have been reported, one study by Arnaud et al., (2002) detected a nonsignificant trend toward poorer cognitive outcomes in carriers of a genetic mutation for brachycephaly (FGFR3 P250R), in comparison with brachycephalic noncarriers of the mutation. In another study, Lajeunie et al., (1998) reported cognitive outcomes were poorest in children with metopic synostosis who had accompanying chromosomal abnormalities (mean IQ=62), followed by those with one or more malformations (e.g. visceral, limb, brain; mean IQ=83) compared with those with isolated metopic synostosis, who performed within normal limits (mean IQ=103).

4.7 Morphological and mechanistic factors

The adverse effects of intracranial hypertension and hydrocephalus upon intellectual outcomes have been supported by clinical experience and experimental studies in craniosynostosis (Bhardwaj & Rohtagi, 1994; Renier & Marchac, 1988; Renier et al., 1982) and other neurosurgical conditions (Dennis et al., 1981).

Renier et al., (1982) compared ICP recordings with psychometric testing in 55 of 75 children with mixed craniosynostoses prior to cranial vault surgery, although the exact nature of intellectual assessment was not specified. A low, but statistically significant relationship was reported between ICP and intelligence, with increased ICP resulting in decreased intelligence. Children with increased ICP who were more than 3 years old had higher rates of intellectual deficit compared to those in whom increased ICP was discovered earlier, which the authors argued supported the idea that the longer the duration of elevated ICP, the greater the effect on intellect. Both lower intelligence and raised ICP were found more frequently in patients with

multiple suture closure, although other factors, such as brain malformations, were acknowledged for their potential contribution to decreased intelligence in these cases.

In a later study, Renier & Marchac (1988) conducted ICP recordings and evaluated intelligence in 300 patients with mixed syndromic and nonsyndromic craniosynostosis. Higher frequencies of intellectual disability were found where more than one suture was synostosed; only 75% of children with brachycephaly and 45% of oxycephaly patients were of normal intelligence. In all types of craniosynostosis except scaphocephaly, IQ was lower in children with intracranial hypertension compared with those without increased pressure, and in older, than younger children. These findings indicate that, at least in coronal suture synostosis, children with raised ICP are at increased risk of cognitive dysfunction.

A contrasting picture was presented by Arnaud et al., (1995), who examined ICP and intellectual outcomes in 396 children with scaphocephaly. The authors found little correlation between ICP and mental level prior to any treatment in 142 children evaluated. They also found higher rates of intellectual disability in patients with normal pressure (6%) compared with normative population estimates, implying that intellectual disabilities may be identified in children with scaphocephaly as they mature, even when intracranial pressure is at normal levels.

With respect to the long-term outcomes of hydrocephalus, Bhardwaj & Rohtagi, (1994)'s longitudinal study compared the intellectual functioning of 50 surgically treated patients with craniosynostosis, with 300 hydrocephalus patients attending an Indian craniosynostosis and hydrocephalus clinic. Craniosynostosis patients were grouped into simple (craniosynostosis and no hydrocephalus or craniofacial syndrome) and complex (craniosynostosis with hydrocephalus and/ or craniofacial syndrome) conditions. Age-appropriate measures of intelligence were administered at 1, 3 and 6 months prior to cranial vault surgery, and at yearly intervals post-surgery. Preoperatively, mental performance was highest in craniosynostosis without hydrocephalus or craniofacial syndrome (mean IQ=97.2), followed by craniosynostosis without hydrocephalus (mean IQ=92.6). Mental performance was poorer where hydrocephalus accompanied craniosynostosis (mean IQ=75.6) than in craniosynostosis without hydrocephalus (mean IQ=81.8). Overall, patients with craniosynostosis also displayed higher postoperative mean IQ scores than the

hydrocephalus patients. Postoperatively, 54% of children with craniosynostosis were of average intelligence (MPQ/IQ >90) compared with 18% of hydrocephalic children. The general findings from this study suggest that craniosynostosis patients have poorer cognitive outcomes when hydrocephalus is present, particularly where their craniosynostosis is syndromic in nature, but that affected individuals still perform, on average, better than hydrocephalic patients who do not have a craniosynostosis condition.

Several works have studied the effects of structural brain malformations upon intellectual functioning. Renier et al., (1996) found no influence of brain malformations (corpus callosum anomalies, ventriculomegaly) upon intellectual development in Apert syndrome, and it is recognised from studies in other populations that agenesis of the corpus callosum can occur without consequences for intellectual functioning where no other malformation is present (Sauerwein & Lassonde, 1994; Strauss, Wada, & Hunter, 1994). However, some have proposed that correlations exist between intellectual dysfunction and other midline structures. In their discussion of a case of Apert syndrome with mental retardation, agenesis of the corpus callosum and limbic malformations, (de Léon et al., 1987) attributed the mental retardation to septum pellucidum defects rather than to the corpus callosum anomalies.

4.8 Surgical Factors

Craniofacial and neurosurgical procedures to correct synostosed sutures carry the inherent risks of any neurosurgical procedure, including intracranial haematomas, seizures and infection (Renier et al., 2000). This risk may be greater in the syndromic craniosynostoses; affected individuals often require multiple surgical procedures over time, the number and intervals between them depending on the individual circumstances of each case.

4.9 Perinatal Risk Factors

Some authors have discounted a relationship between craniosynostosis and intellectual deficiencies by attributing developmental delay to perinatal or medical factors unrelated to the synostosis (Hunter & Rudd, 1977; Hunter, Rudd, & Hoffman, 1976; Noetzel et al., 1985). For example, Abe (1985) attributed mild to

moderate mental retardation in syndromic and nonsyndromic craniosynostosis to perinatal asphyxia or seizures during delivery. However, findings from other studies have contrastedly not found an association between perinatal risk factors and mental development (Kapp-Simon et al., 1993) in nonsyndromic patients.

4.10 Psychosocial Factors and Cognitive Outcomes

Quality of family environment, social support structures and familial history of intellectual impairment has been identified in the literature for its significance upon cognitive outcomes in craniosynostosis and nonclinical populations. Bottero and colleagues (Bottero et al., 1998) reported that 66% of children with trigonocephaly living in suboptimal family environments showed evidence of developmental delay, compared with 26.8% of their sample considered to be from a more stable background. Renier et al., (1996) found that 12.5% of institutionalised patients with Apert syndrome were of normal intelligence, compared with 39.3% of patients with Apert syndrome coming from a 'normal' family background. Authors have similarly stressed the importance of institutionalisation in the genesis of mental retardation in these children (Campis, 1991; Galli, 1976; Patton et al., 1988). Familial history of intellectual deficiencies was attributed to the intellectual disabilities of two sisters with Crouzon syndrome (Noetzel et al., 1985)

Some types of single-suture craniosynostosis are quite disfiguring and should be corrected for cosmetic reasons. Improved craniofacial shape and physical appearance in the craniosynostoses has been shown to be beneficial upon the patients' interaction with parents and their peers, schooling and self-image. Lefebvre et al., (1986) evaluated self-concept and self-rated appearance in children with Apert syndrome and found significant improvements in self-esteem one year after surgery in affected individuals. Such factors can indirectly effect cognitive outcomes with respect to the child's willingness and interest in engaging in school-based activities.

4.11 Psychological Functioning in Craniofacial Anomalies

Health care practitioners working with children with craniosynostosis and other craniofacial anomalies are acutely aware of the many psychological stressors that confront these individuals and their families. These children undergo complex

medical procedures, and frequently suffer functional disabilities due to physical malformations which restrict their capacity to participate in everyday activities to the same level as their non-afflicted peers. The stigma attached to facial and bodily disfigurements can lead to socioemotional problems, and children with craniofacial anomalies are considered at high risk for developing negative self-perceptions withdrawal, social inhibition, anxiety and peer rejection (Rubin & Wilkinson, 1995).

The literature on the psychological aspects of craniofacial anomalies has proliferated in the past several decades (see Speltz, Galbreath, & Greenberg, 1995), examining quite diverse psychological factors and processes, such as the quality of mother-infant relationships (Speltz, Armsden, & Clarren, 1990), children's emotional and behavioural adjustment (Krueckeberg, Kapp-Simon, & Ribordy, 1993; Padwa, Evans, & Pillemer, 1991), self-perception and body-image (Kapp-Simon, Simon, & Kristovich, 1992) and peer relationships (Krueckeberg, Kapp-Simon, & Ribordy, 1993).

The characterization of behavioural features of children with craniofacial disorders has predominantly centred on the cleft lip and/ or palate population, with only small samples of children with craniosynostosis-related disorders included in such samples. Behavioural disorders have commonly been conceptualized in terms of internalising (e.g. shyness, somaticising and depression) and externalising (e.g. disobedience, fighting) problem behaviours. In children aged 3 to 6 years with predominantly cleft lip and/ or palate, but also craniosynostosis and Crouzon syndrome, Krueckeberg et al., (1993) reported no differences in problem behaviour frequency in comparison to a matched control group, based on parent and teacher ratings. However, a longitudinal study on a small group of these children 3 years later revealed clinically significant global behaviour problems in 31% of those studied (Krueckeberg & Kapp-Simon, 1997).

Speltz, Morton, Goodell, & Clarren (1993) measured behavioural functioning in five to seven year old children with mixed craniofacial anomalies, including sagittal synostosis. Measures administered included the parent and teacher versions of a standardised behaviour rating scale, the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF). Four of 23 children (17%) obtained internalising and/

or externalising CBCL scores in the clinically significant range based on both parent and teacher ratings, leading the authors to conclude that children with craniofacial anomalies have at least twice the risk of behaviour problems at school entry than children generally. Gender differences were also evident. Whilst girls with craniofacial anomalies displayed significantly higher behaviour problem frequencies than matched female controls on parent-rated responses to the CBCL, no differences between boys with craniofacial anomalies and a matched male control sample on this measure were found.

Kapp-Simon & Dawson (1998) presented cross-sectional data on 307 children (169 male, 138 female) with craniofacial anomalies aged between 4 and 18 years. Like Speltz et al., (1993), they found elevated rates of problem behaviours in these individuals, with 20% of those evaluated displaying problem behaviours at a clinically significant level.

Running counter to assumptions of psychological impact, cumulative research findings (Clifford, 1983; Endriga & Kapp-Simon, 1999; Sarimski, 2001; Speltz et al., 1995) suggest that as a group, the majority of children with craniofacial anomalies seem to develop in a typical manner and do not experience psychological problems of clinical significance. However, a significant proportion (30% to 40% in most studies) experience some difficulties with internalizing and/or externalizing problems and social competence (Endriga & Kapp-Simon, 1999).

Sarimski (2001) investigated the social and emotional adjustment of 25 school-aged children (ages 5 to 17 years) with Apert syndrome on a German adaptation of the Child Behavior Checklist (Döpfner, Berner, Fleischmann, & Schmidt, 1993). The authors reported that the majority did not present with severe psychological adjustment, although they acknowledged an increased risk of internalising behaviours (social problems and social withdrawal), and peer-relationship difficulties were indicated in more than 50% of children tested. Others (Speltz et al., 1995) have similarly conceded that there does exist a significant subgroup of children with craniofacial anomalies who develop internalising problems, particularly social withdrawal and anxiety.

Whilst children with craniosynostosis confront similar psychological stressors to those with other craniofacial anomalies, their experiences can also differ greatly. For example, many have complex medical problems that require lifelong medical management. The often reported cognitive impairments, particularly in the syndromic craniosynostoses, influence the way children process, interpret and manage interpersonal interactions. Such differences implicate the importance of more specialized investigation into the psychological features of craniosynostosis-specific population samples.

4.12 Summary of Reviewed Literature

A number of general conclusions can be drawn from the literature on the cognitive characteristics of the craniosynostoses to date.

Firstly, the cognitive outcomes of the syndromic craniosynostoses appear to be poorer than that of the nonsyndromic craniosynostoses, and the normative population. However, there appears to be wide cognitive heterogeneity within and between the syndromic craniofacial disorders.

The wide range of frequently reported abnormalities in the syndromic craniosynostoses, which include chromosomal, limb and visceral anomalies and structural brain malformations, contribute to the cognitive heterogeneity in these disorders.

Most studies in the nonsyndromic craniosynostoses suggest that mental development approximates a normal distribution in the early infancy years, which may be interpreted as suggesting that simple craniosynostosis has no major unfavourable outcomes on neuropsychological development.

As children mature, however, there appears to be an increased prevalence of adverse cognitive outcomes in syndromic and nonsyndromic populations. Developmental studies point to an increased incidence of intellectual deficits and specific cognitive and behavioural disturbances in these children as they mature. Furthermore, cognitive deficits in more specialised areas of ability (e.g. attention) may occur in the context of seemingly normal intelligence.

The psychological adjustment literature on the craniosynostoses suggests that in general, children with craniofacial disorders do not present with clinically

significant behavioural disorders. However, these children do appear at increased risk of internalizing and externalizing behavioural problems.

4.13 Methodological Constraints

Generalization and interpretation of the studies presented here depend on any limitation or limitations that may be inherent in clinical research design. In evaluating the significance and drawing inferences about the findings presented in the above studies, one must be mindful of a number of methodological issues, which in some instances, preclude meaningful interpretation and generalization of results.

Firstly, a number of conclusions about the cognitive attributes of infants and children with craniosynostoses, particularly the syndromic craniosynostoses, have been based on anecdotal findings.

Secondly, some studies, predominantly in the syndromic craniosynostoses, are limited by vaguely defined and poorly described methodologies. Whilst small sample sizes are a natural artefact of studying the syndromic craniosynostoses, due the rarity of these conditions, studies are further limited by failing to employ rigorous methodologies in quantifying the cognitive features of these disorders. Information reported appear to be based upon a 'convenience' sample in some instances, and inclusion criteria are seldom specified in such reports.

Studies have also grouped together heterogeneous conditions into single samples; drawing inferences based on group performances as a whole. This includes mixing together different craniofacial disorders (e.g. syndromic and nonsyndromic), combining operated and unoperated cases, including patients with complex medical problems that can confound cognitive outcomes and including wide age ranges in the small samples, which can mask individual differences.

Varying definitions and criteria of normality with respect to intellectual functioning have been defined, which limits the comparability across studies. Some studies have defined normal intelligence by an intellectual quotient (IQ) of at least 90, whilst others have specified this as an IQ of 70 and above.

A significant limitation in the literature to date has been the limiting focus on quantifying intellectual characteristics of the craniosynostoses in making inferences

about functional capabilities in these individuals. The wide range of cognitive abilities in more specialised domains, that have significant implications for everyday adaptive functioning, have not been adequately quantified using rigorous experimental techniques. There have been only two known published studies in the craniosynostoses that have purported to be neuropsychological in nature (Magge et al., 2002; Turtas, Tondi, Tola, Schrbundt Viale, & Martinez, 1993). Neither of these has included *comprehensively* evaluated the range of cognitive domains that typically comprise a neuropsychological assessment, namely attention and concentration, information processing, memory and learning and executive cognitive skills.

The psychological adjustment literature on craniofacial anomalies has been limited by its focus on the cleft lip and/ or palate population, with children with craniosynostosis comprising only small subsamples amongst other craniofacial disorders (e.g. Krueckeberg et al., 1993; Speltz et al., 1993). The long-term adjustment issues in craniosynostosis-specific populations are, furthermore, seldom studied, and warrant investigation in a more specialized way.

4.14 Aims and Hypotheses

The purpose of the present research was to address some of the limitations of the earlier literature on craniosynostosis and document the long-term neuropsychological outcomes in children and adolescents with craniofacial disorders. Children diagnosed with syndromic and nonsyndromic craniosynostosis who had undergone surgical correction for their condition comprised the study population. This sample was older than that of many previous studies (age range 7 to 16 years), so that specialized cognitive skills could be evaluated using more precise psychometric tools.

Due to the paucity of research characterising the wide spectrum of neuropsychological abilities in children and adolescents with craniosynostosis, this was primarily an exploratory study, aimed at comprehensively describing the abilities of these children with respect to intelligence and more specialized cognitive skills. As such, the study hypotheses remained broad. It was predicted that children with syndromic craniosynostosis (SC) would display lower mean global intellectual abilities than those with nonsyndromic craniosynostosis (NSC),

and that of normative population data. It was predicted that the intellectual abilities of those with NSC would not significantly differ from that of the normative population.

With respect to more specific cognitive domains, namely, information processing, memory and new learning, attention and executive functioning, it was predicted that the SC sample would display below average abilities in these skills, that is, at a level commensurate with their intellectual capabilities. On the basis of previous literature that has suggested subtle signs of cognitive dysfunction in school-aged samples of nonsyndromic craniosynostosis (e.g. learning disabilities, ADHD), it was hypothesised that the NSC group would also display below average abilities in specialized cognitive skills.

Chapter Five

5 Research Design

5.1 Participant Recruitment

5.1.1 Sample Selection

Patients were ascertained through the Dept of Plastic and Maxillofacial Surgery and Health Information Services patient records of the Royal Children's Hospital (RCH). The RCH is a major tertiary referral centre for craniosynostosis and receives patients from all parts of Australasia and internationally. All invited patients were residing in the Melbourne metropolitan area or living in regional Victoria. All patients who were aged between 7 and 16 years 11 months at the time of recruitment, and who met diagnostic criteria for craniosynostosis, were eligible to participate. The study was approved by the Ethics Committees of the participating institutions (Victoria University, Royal Children's Hospital).

5.1.2 Diagnostic Classification

The Australian Version of the International Classification of Diseases- 9th Revision, Clinical Modification (ICD-9-CM) and the updated International Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) diagnostic classifications systems were used to identify the various craniosynostosis subtypes from the hospital medical records (Appendix B). The ICD-9-CM and ICD-10-AM are based on, and compatible with their parent systems; the World Health Organisation's 9th and 10th Revisions of the International Classification of Diseases (ICD-9 and ICD-10). These systems provide morbidity and mortality information and coding systems of diseases. The same Psychologist reviewed medical files of patients with craniosynostosis. Those satisfying age and other specified inclusionary criteria were then reviewed by the Clinical Geneticist.

5.1.3 Diagnostic Verification

The same Clinical Geneticist systematically reviewed the hospital medical records of patients with craniosynostosis for details of the specific cranial suture/s involved, clinical phenotypic characteristics and radiological findings to assure diagnosis and confirm diagnostic classificatory group. Findings from genetics testing and/ or consultations, where performed were also reviewed during this process.

5.1.4 Inclusion/ Exclusion Criteria

The following exclusionary criteria applied in sample selection:

(i) Patients living outside of the State of Victoria, Australia.

(ii) Patients with deformational (or positional) plagiocephaly or unoperated craniosynostosis

(iii) Patients with secondary craniosynostosis, i.e. craniosynostosis secondary to another medical condition

(iv) Age less than 7 years 0 months or greater than 16 years 11 months at the time of neuropsychological assessment

(v) Presence of additional neurologic factors that may have confounded neuropsychological outcomes. These included the presence of a seizure disorder, traumatic brain injury or intraoperative complications.

5.2 Sample Characteristics

Two experimental groups comprised the broader craniosynostosis sample. Selected patients had undergone one or more operations to separate the fused cranial suture/s. Participants were classified into syndromic or nonsyndromic conditions; the series was further classified according to the various subtypes of craniosynostosis. A small number of participants (n=2) underwent initial cranial release surgery at hospitals other than the RCH, but had attended the RCH in relation to their condition since that time.

5.2.1 Participants

A total of 38 participants with craniosynostosis were enrolled in this prospective study between January and October 2002. Of these, two patients subsequently withdrew from the study; one patient with Apert syndrome withdrew due to medical commitments, one participant with nonsyndromic unicoronal craniosynostosis withdrew for personal reasons. Two other children were excluded from the study following neuropsychological assessment. A child with Crouzon syndrome displayed a cognitive profile suggestive of a history of head trauma, within the context of a reportedly non-consequential fall. A child with metopic synostosis was deemed to have a severely impoverished social and environmental upbringing. With respect to the latter two participants, it was considered that, these factors might have negatively biased performances on cognitive measures beyond that potentially attributable to their diagnosis, and thus to be conservative, their data was not reported on in the statistical analyses presented here.

The final sample of 34 participants comprised 13 cases of well-delineated syndromes representing the syndromic craniosynostoses (Experimental Group 1) and 21 cases of nonsyndromic craniosynostosis (Experimental Group 2). Table 5.1 shows sample characteristics. This group of children ranged from 7.1 years to 15.8 years of age (mean age=10.9 years, *SD* =2.5years) at the time of neuropsychological assessment. There were more males (57.1%, n=20) than females (42.9%) in the whole sample. Socioeconomic status (SES) was estimated on the basis of the principal income earner of the family, and quantified using the Daniel's Scale of Occupational Prestige (Daniel, 1983) which provides a 7-point rating scale, with higher scores denoting lower SES. The mean SES of the syndromic (M=4.3, SD=1.37) and nonsyndromic (M=4.4, SD=1.34) groups did not significantly differ, t=.086, p=.932.

5.2.1.1 Control Group

This study did not include a control group. Normative population data was used to compare participant performances.

Table 5-1 Participant sample characteristics for the syndromic and nonsyndromic groups

Syndromic Craniosynostoses (n=13)				Nonsyndromic Craniosynostoses (n=21)			
	Total 'n'	**% group**	**% sample**		**Total 'n'**	**% group**	**% sample**
Apert Syndrome	3	23.1	8.6	Unicoronal [right/ left-sided] synostosis	6	28.6	17.6
Crouzon Syndrome	3	23.1	8.6	Sagittal synostosis	6	28.6	17.6
Saethre-Chotzen Syndrome	5	38.5	14.3	Metopic synostosis	3	14.3	8.8
Pfeiffer Syndrome	1	7.7	2.9	Lambdoid synostosis	3	14.3	8.8
Other-Witkop Syndrome	1	7.7	2.9	Multisutural synostosis	3	13.6	8.8
Total	13	100.0	38.2	Total	21	100.0	61.8

5.3 Materials

5.3.1 Examiner Characteristics

All children were assessed by the same licensed psychologist. The psychologist had formal graduate training in psychological assessment, and was experienced in the administration and interpretation of the clinical instruments used in the assessment.

5.3.2 Assessment Instruments

A range of standardised neuropsychological/ psychological assessment measures were selected for use in the current study. The general psychometric properties, reliability and validity of all selected instruments have been well-demonstrated. Selected measures are briefly described below.

5.3.2.1 *Wechsler Intelligence Scale for Children- Third Edition (WISC-III; Wechsler, 1992)*

The WISC-III is a standardised measure that establishes indices of general intellectual function, comprising verbal intelligence and non-verbal (visual-spatial) intelligence. Designed for children between 6 years to 16 years and 11 months of age, the WISC-III is one of the most widely administered tests of intellectual functioning. The measure yields information about the presence or absence of intellectual disability, and provides clues to altered function (Lezak, 1995). Numerous sources attest to the scales sound psychometric properties (e.g. Spreen & Strauss, 1998; Wechsler, 1992). Reliability coefficients range between 0.91 and 0.96 for the verbal, performance and full-scale IQ index scores. Multiple sources of evidence of the validity of this scale have been provided.

Administration of the test involves the examiner posing questions to the subject, displaying pictures or puzzles, and recording responses in a response booklet. Raw score conversion and factor-based index scores were derived following the procedures outlined in the scoring and interpretation guidelines of the manual for the WISC-III (Wechsler, 1992). For each of the 11 subtests administered, raw scores were converted to scale scores on the basis of the distribution of that person's age group's, with a mean of 10 and a standard deviation of 3. Full scale, Verbal and Performance (nonverbal) intellectual quotients, as well as three of four possible factor-based index scores (Verbal Comprehension, Perceptual Organisation and Freedom from Distractibility), were also calculated from subtest scores. Each of the distributions of the Verbal, Performance and Full Scale IQ scores and the three index scores has a mean of 100 and a standard deviation of 15. A score of 100 denotes the performance of the average child of a given age on that scale. Scores of 85 and 115 correspond to 1 standard deviation below and above the mean respectively.

5.3.2.2 *Leiter International Performance Scale-Revised (Leiter-R; Roid & Miller, 1997)*

The Leiter-R is an individually administered test designed to test cognitive functions in children and adolescents aged 2 years to 20 years. The battery includes measures of nonverbal intelligence in fluid reasoning and visualization, as well as appraisals of visuospatial memory and attention. It was developed to provide a

nonverbal memory of intellectual ability, memory and attention that can be used to assess individuals with a variety of difficulties, including communication disorders, cognitive delay and traumatic brain injury. The Leiter-R comprises two subtest groupings: the Visualisation and Reasoning battery and the Attention and Memory battery. Subtests from the VR battery are used to estimate intellectual ability. A Brief IQ screener was used which comprises a brief collection of 4 of the 10 subtests of the VR battery and provides an estimate of global intellectual level as classified. The Brief IQ screener has been shown to have high reliability (range 0.88 to 0.90 across age groups assessed; Roid & Miller, 1997). These subtests have been demonstrated to have high internal consistency (average reliability ranged from 0.75 to 0.88 across age groups studied). The Brief IQ screener score has also been demonstrated to correlate at a consistently high level with the WISC-III Full scale IQ (r=.85) and the Performance IQ (r=.85; Roid & Miller, 1997).

5.3.2.3 Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999)

The TEA-Ch is a standardized and normed clinical battery for children that allows for relative assessment across various dimensions of attentional ability. The subtests measure how well children can focus attentional resources and sustain attentional focus to achieve goals that will be useful for them. The TEA-Ch has been demonstrated to have sound reliability and validity (Manly et al., 1999). Three subtests measuring focused attention, sustained/ divided attention and processing speed/reaction time were selected for inclusion in the current test protocol.

The TEA-Ch has been standardized on a sample of 293 Australian children and adolescents between the ages of 6 and 16 years of age. Raw test scores were converted into standard scores (age scaled), which had an age mean of 10 and standard deviation of 3.

i) Sky Search Attention and Sky Search Motor Control

The sky search subtest examines selective attention. The Sky Search Attention task evaluated the capacity to attend to relevant information whilst rejecting irrelevant information. Examinees were instructed to detect as many same pair 'spaceships' as possible on a sheet of very similar and distracting pairs of dissimilar spaceships, circling them with a pen. The Sky Search Motor Control subtest provided an

estimate of speed of processing. Here, the sheet contained no distracting spaceships. The time taken and number of circled same ship pairs were recorded in each part of the test. By subtracting part 2 from part 1, this test enabled a measure of processing speed and reaction time, which may be related to attention deficits, that was relatively free from the influence of motor slowness.

ii) Sky Search DT

This task measures sustained-divided attention; the capacity to maintain attentional focus, as well as divide attentional resources between competing mental demands. Having previously completed the Sky Search subtest the examinee is asked to combine dual task demands. These involve finding the target spaceships on the sheet whilst simultaneously counting a number of recorded scoring sounds over a series of trials. The number of correctly identified ship pairs, time taken and correctly counted scoring sounds are recorded. Raw scores on all TEA-Ch subtests are converted to age-scaled standard scores, in accordance with the guidelines outlined in the manual.

5.3.2.4 Children's Memory Scale (CMS; M.J. Cohen, 1997)

The children's memory scale provides measures of various aspects of memory function. In the current protocol, subtests measuring learning and retention of verbal and visual-spatial material were assessed. Reliability of the measure is supported by reliability coefficient scores ranging from 0.54 (Dot Locations short delay), with most subtests ranging between 0.73 and 0.86 for those age groups and subtests studied. Convergent, divergent and construct validity of the subtests in the CMS has also been indicated, and inter-rater consistency is very high (M.J. Cohen, 1997).

i) Dot Locations

The Dot Locations subtest provides an assessment of the child's ability to learn and recall the spatial location of the same dot pattern over three learning trials, by reproducing the dot pattern presented on a stimulus card using chips on a response grid. An interference task involves the presentation of a stimulus card with red dots in a different spatial location is presented following the three learning trials. An immediate recall trial is administered immediately after the interference task. A delayed recall trial is administered 25-35 minutes later. The number of correctly

placed chips on the three learning trials is summed, comprising a learning score. Correct placement on the immediate recall and delayed recall trials are also recorded.

ii) Word Lists

This subtest assesses the subject's ability to process, learn, and recall a list of unrelated words over a series of four trials. After the initial presentation of the whole word list, the subject is selectively reminded of only those words which he/ she did not recall on the previous presentation. This requires that the child impose a self-organisation strategy in order to learn and recall the word list in the most efficient manner. This subtest provides measures of learning, delayed auditory-verbal memory function and delayed recognition recall.

5.3.2.5 Neuropsychological Assessment of the School-Aged Child (NASAC; V. Anderson, Lajoie, & Bell, 1996)

This test battery comprises a range of well-recognised tests that have been standardised on a sample of Australian children aged between 7 and 13 years. Test scores were compared with means and standard deviations of examinee's age-matched peers.

i) Block Span

This is a test of immediate memory for visual-spatial material, involving presentation of an array of nine identical blocks. The examinee was required to tap a sequence of blocks of increasing length as demonstrated by the examiner, commencing with a sequence of three blocks. The maximum number of blocks correctly tapped in sequence was recorded.

ii) Complex Figure of Rey Test (CFRT; Rey, 1964)

The test permits assessment of a variety of cognitive processes, including planning and organisational skills, problem-solving strategies, as well as memory, perceptual and motor functions (Meyers & Meyers, 1995; Waber & Holmes, 1986). Subjects are required to copy the CFRT, a complex geometric design, being given a series of different coloured pens during the process of drawing. The order in which sections of the design were reproduced, and total time taken were recorded. The child was asked to draw the design from memory after a five-minute period (delay), during which time a different test (Verbal Fluency task) was administered. Accuracy was

scored according to Lezak (1993). The rating scale of P. Anderson, V. Anderson, & Garth (2001) was used to rate organisational ability, ranging between 1 (unrecognisable) and 7 (excellent organisation).

iii) Story Recall

This is a test of short-term memory for verbal material. Children were read two stories, modified from Luria's Neuropsychological Battery (Christensen, 1979), describing episodes relevant to a school-aged population. After presentation of each passage, children were asked to retell the story in their own words. Each story was divided into 22 chunks, with recall of each chunk scored as one point. Half-points were awarded where only one part of a chunk was recalled or when meaning was evident but different wording was used. Children were asked to spontaneously recall the stories after a thirty-minute interval. Recall scores for each story and a total recall score were computed for the immediate recall and delayed recall trials.

iv) Verbal Fluency (Gaddes & Crockett, 1975)

This task evaluates the spontaneous production of words beginning with a particular letter under time restraints. It measures executive aspects of language processing, specifically verbal fluency-concept formation, abstract thinking and the ability to simultaneously remember two rules and to shift response set as required. Children were instructed that they had 60 seconds to think of all the words they could, beginning with the specified letter. They were told to follow a number of rules, including not using words beginning with capital letters (e.g. people's names, place names), and that they must say different words each time. Trials were administered for each of three letters 'F', 'A', and 'S'. The number of admissible words generated, errors and rule breaks were recorded and analysed.

v) Tower of London

The Tower of London (Shallice, 1982) is a task measuring planning and problem solving ability. The child is presented with 3 coloured balls arranged on 3 sticks of differing heights in a series of problem-solving situations. Children were required to match the bead configuration presented on the stimulus card in a prescribed number of moves, whilst adhering to a set of specified rules and within a time limit. 12 stimulus items were presented, of increasing task difficulty. Administration and scoring were according to V. Anderson et al., (1996), and generated the following

measures: number of problems correctly solved, number of failed attempts, and summary score.

5.3.2.6 *Wide Range Achievement Test- 3rd Edition (WRAT-3; Wilkinson, 1993)*

i) Reading subtest

The WRAT-3 is one of the most frequently used measures of academic achievement, including reading, spelling and arithmetic skills. There are two alternate forms in the third edition of the test; the Blue test form was administered to subjects in the current study. The reading subtest of the WRAT-3 measures letter and word recognition and pronunciation. The examiner presented a test card with a list of 15 letters and 42 words to the subject, who was instructed to read their responses out loud. Individuals 7 years and younger were asked to read the letters followed by the list of words. For those aged 8 years and older who were able to successfully read five or more of the word items, the preliminary section of 15 letters was not administered. The total number of correct responses was recorded, and raw scores converted to standard scores and age-equivalent scores.

5.3.2.7 *Child Behaviour Checklist -Parent (Child Behaviour Checklist; CBCL) for Ages 5-18 (Achenbach, 1991) and Teacher Report Form (TRF) for Ages 5-18 (Achenbach, 1991)*

The Child Behaviour Checklist and Teacher Report Form provide an assessment of child problem-behaviour frequency based on parent report, and teacher report, respectively. Parents and teachers were asked to complete a questionnaire, in which they rated the approximate frequency of 113 child problem behaviours over the preceding 6 months using the following ratings: '0' 'Not true', '1' 'Somewhat or Sometimes true' or '2' 'Very true or Often true'. The CBCL and TRF provide age and gender-specific individual subscale T-scores for particular kinds of problems (social withdrawal, somatic complaints, anxiety, social problems, thought problems, attention difficulties, antisocial behaviour, and aggression) as well as composite T-scores for internalizing, externalising and total problems. A T-score of 65 and over on individual and composite scales is defined as 'clinically significant' according to manual interpretation guidelines.

A summary of the components measured by the various neuropsychological test measures is presented in Table 5.1.

Table 5-2 Components measured by neuropsychological test instruments

Components	**Neuropsychological Test Measures**
Global intellectual functioning Verbal intellectual functioning Nonverbal intellectual functioning	1. Full Scale Intellectual Quotient 2. Verbal Intellectual Quotient 3. Performance Intellectual Quotient
Selective Attention	1. Sky Search: Attention score
Sustained/ Divided Attention	1. Sky Search: Dual Task score
Immediate memory span/ Information processing	1. Digit Span 2. Block Span
Planning and problem-solving	1. Tower of London: total summary score
Visuospatial construction and planning Visual organisation	1. Rey Figure Accuracy score 2. Rey Figure Organisational rating
Visual memory and learning	1. Dot Locations: learning score 2. Dot Locations: delayed recall score
Verbal memory and new learning	1. Word Lists: learning score 2. Word Lists: delayed recall score 3. Story recall: immediate recall total score 4. Story recall: delayed recall total score
Reading	1. Reading standard score
Social and Behavioural functioning	1. Child Behavior Checklist

5.3.2.8 Neuropsychological Interview Form

Parents/ guardians were asked to complete a structured questionnaire (Appendix C) addressing the following variables:

- Social and demographic information(e.g. ethnic grouping, birth order, number of siblings, parental age, handedness, family history of learning difficulties

- Pregnancy and birth
- Developmental milestones
- Medical history
- Academic functioning
- Psychosocial functioning

This questionnaire was developed by the researchers, based on clinical experience and information typically obtained in completing a neuropsychological assessment. This is a non-standardised assessment tool.

5.4 Procedure

5.4.1 Recruitment

After identifying eligible patients from RCH medical records, Parent/ Guardian Information Sheets (Appendix D) were sent to parents/ guardians of potential participants. Participant Information Sheets (Appendix E) were also included for those over the age of 12 years. A cover letter introducing the study included a tear-off slip for parents to register their interest for their child's participation in the study, and prepaid envelope for return of the reply slips to the Principal Researcher. A total of 92 letters of invitation were sent to eligible families. Upon receipt of tear-off slips, the Principal Researcher contacted the parent/ guardian to arrange an assessment date, and provide further information about the study, where requested. A letter of confirmation was sent to these prospective participants, containing details of the agreed location of the assessment session/s and appointment date and time.

Of the 92 invitation letters of invitation sent, nine families were not able to be located, as indicated by return of letters to the sender. Thirty six parents registered their child to participate in the study by returning the reply slip or contacting the researchers directly by telephone, comprising a response rate of 39%. It was considered important to verify the status of non-responders, since many individuals may not have attended for follow-up or other treatment at the RCH since their infancy years. Due to the small sample size, all parents of individuals diagnosed with syndromic craniosynostosis who did not respond to the letter of invitation were contacted. A random sample of parents of children with nonsyndromic

craniosynostosis were also contacted to clarify their interest in the study. Two participants, one with syndromic craniosynostosis and another with nonsyndromic were enrolled into the study following telephone contact. Comparison of responders and non-responders on the basis of information contained in medical records suggested no notable differences in terms of child age, sex or clinical prognosis/ severity. Therefore the final study sample was considered representative of the target population.

5.4.2 Assessment Format

The neuropsychological assessment and parent interview was typically conducted on one day or two half-day sessions; the duration varying according to participants' capabilities. The assessment involved consecutive test administration sessions of between 30-45 minutes duration, with interval rest periods of 15-30 minutes as required. A 45-60 minute lunch period was also incorporated into the single day assessment sessions.

The participant and a parent/ guardian attended for the appointment. The format of the assessment process was explained. The structure of the session as well as assessment measures administered was modified, as appropriate, to accommodate the cognitive, behavioural and physical capabilities of participants. Parents and participants (where appropriate), were requested to sign a consent form (Appendices F, G) confirming their agreement to participate in the study. Parents were briefly questioned in a semi-structured interview format to gather information about the child's current schooling activities and behaviour of participants, and information that may have been relevant to the neuropsychological assessment (e.g. hearing/ vision difficulties).

5.4.3 Parent questionnaires

Whilst participants completed the neuropsychological assessment, parents were asked to complete the following:

i) Neuropsychological Interview Form

ii) Child Behaviour Checklist- Parent form

iii) Consent form addressed to the participant's main school teacher, which permitted the researcher to send the teacher the TRF form questionnaire.

5.4.4 Neuropsychological assessment

Participants were typically administered the neuropsychological measures in the following sequence:

- WISC-III
- Rey Complex Figure
- Verbal Fluency
- Rey Complex Figure (5 minute delay)
- CMS- Word Lists
- CMS- Dot Locations
- Story Recall
- Block Span
- Word Lists-delayed recall
- Dot Locations- delayed recall
- Story recall- delayed recall
- TEA-Ch subtests
- WRAT-3 Reading subtest
- Tower of London

To avoid undue distress, omission of tests occurred where subjects were deemed incapable of performing tasks due to mental and/ or physical impairments. This occurred for two subjects with syndromic craniosynostosis.

5.4.4.1 Modified Assessment

The standard assessment protocol was judged to be unsuitable for one participant, whose expressive language skills were limited. An alternate measure of intellectual functioning was substituted; the Leiter International Performance Scale-Revised (selected subtests). This assessment tool relies predominantly on nonverbal modes of communication to assess comprehension, perceptual reasoning and problem-solving through visually presented materials. A brief intellectual quotient (IQ) estimate was obtained from subtests administered. The participant's parents were also interviewed on the Vineland Adaptive Behaviour Scales-Interview Edition Survey Form (Sparrow & Cicchetti, 1984) to enable evaluation of the child's social and adaptive abilities of daily living.

5.4.5 Feedback

A feedback session with parent(s)/ guardian(s) and, where deemed appropriate, individual participants, was scheduled upon completion of the neuropsychological assessment. This session outlined individual participant's cognitive strengths and weaknesses on testing, and was conducted under the supervision of the Clinical Neuropsychologist/ Associate Investigator involved in the project. A neuropsychology report providing a written summary of the neuropsychological assessment findings for participants was completed where requested by their parents.

Chapter Six

6 Results

6.1 Data Screening and Statistical Analyses

Data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 11.5. Univariate descriptive statistics were used to describe demographic characteristics of the sample, intellectual quotients (IQ) and other cognitive domains of interest; attention, memory and new learning and executive functioning. Analysis of variance (univariate and multivariate) was employed to investigate the diagnostic group (syndromic, SC; nonsyndromic, NSC) differences in IQ variables. Additional MANOVA were then employed to examine group differences on variables in the cognitive domains of attention, memory and new learning and executive cognitive processes. Independent sample t-tests were employed to test group differences from the normative distribution in specific cognitive domains. Paired samples t-tests and repeated measures ANOVA's were used to examine within-group differences. An alpha level of .05 was used for all statistical tests.

6.1.1 Data Screening

Prior to analyses, variables of interest were examined through various SPSS programs for accuracy of data entry, missing values, plausible means and standard deviations, detection of outliers, fit between distributions and the assumptions of univariate and multivariate analyses. The variables of interest were demographic characteristics, intellectual outcome measures and variables assessing attention, memory and new learning, reading and executive cognitive skills.

6.1.1.1 Data accuracy

Data accuracy was verified by double-scoring raw data prior to data entry. The accuracy of the SPSS data file was checked by cross-verification of raw data, viewing data and performing frequency counts to detect anomalous values.

6.1.1.2 Missing Data

Missing data were identified on all cognitive assessment variables and one demographic variable (SES occupation); the highest frequency of missing values for any one variable was 5 cases. The following procedures were employed in the treatment of missing data:

i) True missing values due to, e.g. incomplete raw data, were coded as '-1' and these cases were excluded on a listwise basis from statistical analyses.

ii) Three subjects were deemed incapable of undertaking the full battery of cognitive assessment tasks due to their cognitive limitations. This determination was based on the subjects' performance on intellectual assessment (all subjects completed a measure of intellectual functioning) as well as historical information about their capabilities. On ethical grounds, the entire assessment battery was not administered to these participants to avoid undue distress. In these cases, missing data on non-completed tests was substituted with the lowest standard score obtainable for any given test; typically equivalent to 2 standard deviations below the normative population mean. This was considered consistent with the intellectual abilities of these subjects. Other options for handling these missing values, such as replacing with a group mean were considered, but would have resulted in inflated and thus non-representative estimate of the subjects' actual capabilities. Simply deleting these cases from the analyses was not viable due to the small sample size and resultant impact upon statistical power.

6.1.1.3 Detection of Outliers

Univariate descriptive statistics and histograms were undertaken using SPSS frequencies program to check whether the distribution of scores for all individual variables were within the expected ranges. For test variables (i.e. intellectual and other cognitive variables), a z-score or standard score value of three or more standard deviations from the normal distribution mean was classified as an outlier. The following outlines the treatment of outliers.

A full scale intellectual quotient index score of 44 for one case with syndromic craniosynostosis was detected upon data screening procedures. This score fell

within 2 standard deviations of the mean full scale IQ score of 83.1 (standard deviation=21.9) of the SC group, and representative of the general intellectual capabilities of this population, and thus not subject to treatment as an outlier in the data analysis.

Dot Locations. One outlier on the Dot Locations delayed recall variable, in which the transformed z-score on the Dot Locations delayed recall variable was > 3 standard deviations below the mean and associated with a non-normal skewness (z-score=-3.94) was detected. To counteract the skew and obtain a closer approximation to a normal distribution, the original standard score value (2 from a mean of 10; standard deviation of 3) was increased to a score of 4. This transformed to a z-score of -2.00. Tests of normality based on skewness and kurtosis improved the skewness z-score statistic to –3.00 from –3.94, and kurtosis z-score statistic to 1.26 from 3.74, providing a closer approximation to a normal distribution than previously obtained.

Reading z-score. The z-score for the reading subtest was shown to be within acceptable limits for skewness and kurtosis for the composite group and the syndromic group. However, non-normal skewness and kurtosis was detected for the nonsyndromic group in which one case was associated with a z-score of greater than 3 standard deviations below the mean (z=–3.40). A z-score value of –3.00 was assigned to this case. This improved skewness from z=–4.41 to –4.02 and kurtosis from 5.70 to 4.63 providing a closer approximation to a normal distribution.

6.1.1.4 Univariate Normality Tests

To test that assumptions such as normality of distributions and heterogeneity of variance of statistical tests were met, skewness and kurtosis values were examined for each of the diagnostic groups.

Normality tests showed that the distribution of scores for verbal, nonverbal and full-scale IQ's were not significantly different from normal for the diagnostic groups.

6.1.1.5 Multivariate Normality, Linearity and Homoscedasticity

Multivariate normality was also checked by screening continuous variables and conducting linear regression analysis using Mahalanobis' distance on variables of interest in the analyses and their linear combinations.

6.1.1.6 Multicollinearity and Singularity

Since the FSIQ index score is derived from the verbal and performance IQ subtest scores, and thus conceptually related, FSIQ was examined in separate MANOVA analyses to the VIQ and PIQ variables to avoid multicollinearity of scores. The index scores of Verbal Comprehension, Perceptual Organisation and Freedom from Distractibility, which are also derived from combinations of the WISC-III subtests, were treated in the same manner.

6.2 Intellectual Functioning

Two measures of intellectual functioning (IQ) were used to describe the intellectual abilities in the 34 subjects of the final sample. The WISC-III (see section 5.3.2.1) was administered to 32 subjects. One subject who had been evaluated on this measure two months prior to participating in the study was not re-assessed on this instrument due to test-retest effects. Instead, raw test data from the previous administration was entered into the current dataset. The Leiter-R was administered to one subject whose severe expressive language deficits limited her capacity to provide the verbal responses required on the WISC-III. A 'Brief IQ screener score' was obtained on the Leiter-R. This score is correlated at a consistently high level with the WISC-III Full Scale IQ (r=.85) and hence substituted for a full scale IQ score in the data analyses.

6.2.1 Statistical Analyses

Groups were compared on the three main indices of intellectual functioning: general (full scale intelligence quotient; FSIQ), verbal (verbal intelligence quotient; VIQ) and nonverbal (performance intelligence quotient; PIQ) as well as on the three factor-based indices: Verbal Comprehension (VC), Perceptual Organisation (PO) and Freedom from Distractibility (FD). Results of descriptive analyses have been presented in Table 6.1.

6.2.2 Group Comparison on Intellectual functioning

Univariate analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) procedures were used to test the significance of group differences on the index-based domains of intellectual functioning. Results of evaluation of assumptions of normality, homogeneity of variances, linearity and multicollinearity, where appropriate, were satisfactory for these procedures. As index-based IQ scores are derived from various combinations of the same subtests of the WISC-III, and thus conceptually related, three separate ANOVA procedures were performed. Univariate F-statistics and significance p values from these comparisons have been summarised in Table 6.1.

Global intellectual functioning (FSIQ) is derived from the verbal and performance scales and hence group differences on this score were examined using a univariate *F*-test ANOVA procedure, with FSIQ as the within-subject dependent variable and diagnostic group as the independent variable. An inspection of Table 6.1 reveals that the mean FSIQ of the NSC group was higher than that of the SC group. The results of the univariate ANOVA showed that this difference was statistically significant ($F(1,32)=10.40, p<.01$).

Group differences on the verbal and nonverbal IQ indices were then examined. A 1 x 2 MANOVA was performed on two within-subjects dependent variables: verbal (VIQ) and performance (PIQ), with diagnostic group (SC, NSC) forming the independent variable. Total N was reduced to 33 with the deletion of a case missing a value on both dependent variables. This analysis showed that the combined dependent variables were significantly affected by diagnostic group, (*Wilks'* $\lambda=0.789$, $F(2,30)=4.012$, $p<.05$). The mean verbal and nonverbal intellectual abilities were significantly higher in the NSC group than the SC group, with the dependent variable that best distinguished the groups being VIQ, $F(1,31)=7.75$, $p<.01$.

A MANOVA was then performed to examine group differences on the three factor-based indices of intellectual functioning: verbal comprehension, freedom from distractibility and perceptual organisation. These three within-subjects variables were entered as dependent variables, and diagnostic group (SC, NSC) was entered as the independent variable. Total N was reduced to 33 with the deletion of a case missing a score on each of the dependent variables. The main effect of the combined dependent variables for this model was approaching significance, (*Wilks'* $\lambda=.795$, $F(3,29)=2.49$, $p=.080$). Closer inspection of the data revealed that the verbal comprehension factor made a unique contribution to the model, $F(1,31)=7.05$, $p<.05$ but no significant effect was observed for the perceptual organisation, $F(1,31)=4.00$, $p=.054$, nor the freedom from distractibility factors, $F(1,31)=1.73, p=.198$.

Table 6-1 Descriptive statistics and ANOVA results comparing syndromic and nonsyndromic groups on indices of intellectual functioning

Intelligence Quotient (IQ) Index Scale	Craniosynostosis Group				Significance tests	
	Syndromic (n=13)		Nonsyndromic (n=21)			
	Mean (SD)	*Range*	*Mean (SD)*	*Range*	*F*	*p*
Full Scale IQ	83.1 (21.9)	44-116	103.4 (14.9)	83-143	10.40	.003**
Verbal IQ	85.5 (22.9)	52-133	102.9 (13.1)	81-131	7.75	.009**
Performance IQ	89.7 (16.5)	54-120	103.6 (16.9)	82-148	5.28	.028*
Verbal Comprehension	85.8 (22.2)	50-130	101.8 (12.6)	81-131	7.05	.012*
Perceptual Organisation	91.7 (15.8)	51-114	103.5 (16.7)	83-144	4.00	.054
Freedom from Distractibility	96.2 (21.1)	64-134	104.7 (15.8)	75-142	1.73	.198

**$p<.01$, *$p<.05$

6.2.3 Age, Gender and Surgical Factors

Three univariate ANOVA procedures were performed to examine the effects of gender, age and age at surgery on global intellectual functioning (FSIQ).

6.2.3.1 Gender

Results of univariate ANOVA with gender comprising the dependent variable revealed non-significant differences, $F(1,32)=.49$, $p=.489$, between the global intellectual abilities of males ($M=97.8$, $SD=16.9$) and females ($M=92.9$, $SD=24.2$).

6.2.3.2 *Age*

The influence of age at assessment and intellectual outcomes was examined. Subjects were divided into two age groups; 11 years or less (n=16) and 12 years and over (n=18). Age-based categories were classified according to primary school and secondary school age ranges. Results of one-way ANOVA revealed that the mean FSIQ of subjects aged 11 years or less (M=98.1, SD=22.2) and that of subjects aged 12 years or more (M=93.4, SD=18.6) did not significantly differ, $F(1,32)=.48$, $p=.504$.

6.2.3.3 *Age at Surgery*

The mean age at the time of initial cranial expansion surgery for the study sample was 7.6 months (SD=6.8 months) and ranged between 2 weeks to 29 months. The influence of age at time of surgery was examined in relation to intellectual outcomes. Subjects were divided into early (cranial release surgery at <12 months of age; n=27) and late (cranial release surgery at > 12 months of age; n=5) operative groups. A cutoff time-based classification of 365 days was based on clinical factors (approximate age at which the child's skull becomes rigid) and those delineated in previous experimental studies (e.g. Bottero et al., 1998; Kapp-Simon, 1998). Results of one-way ANOVA showed that the mean FSIQ of the early operative (M=98.3, SD=18.2) and late operative groups (M=93.0, SD=27.0) did not significantly differ, $F(1,30)=.30$, $p=.586$, and suggest that intellectual outcomes were not significantly better in those undergoing cranial vault expansion before 12 months of age compared to those operated on after that time.

6.2.4 *Intellectual functioning comparisons with the theoretical normal curve*

Intellectual disability was defined on the basis of ICD-10 diagnostic criteria as an intellectual quotient (IQ) standard score of <70 on the Full Scale Intellectual Quotient (FSIQ) scale of the WISC-III and the Brief IQ screener standard score on the LIPS-R.

The study sample was characterised by a wide spread of intellectual abilities, ranging from a low FSIQ of 44 to a high of 143, representing standard scores of ± 2 standard deviations from the normal population mean and consistent with diagnostic classifications of moderate mental retardation to very superior intellectual ability.

The mean FSIQ for the composite group (N=34) was 95.6 (20.2), which falls within the 'average' range of general intelligence according to WISC-III classification criteria and within normal limits according to ICD-10 (World Health Organisation, 1992) classifications for intellectual ability. The distribution of FSIQ scores was compared to that predicted according to the theoretical normal curve and presented in Table 6.2. Sixty percent of the study sample performed within the average range of intelligence, which is slightly higher than predicted population rates of 50%. Trends toward lower FSIQ scores appear largely attributable to the SC group, of whom nearly 50% showed below average FSIQ scores compared with expected rates of 25% (skewness=-.052, kurtosis=-0.66). In contrast, higher than predicted proportions (90.5% versus 75.0%) of the NSC group were performing at or above the average range of intelligence (skewness=1.06, kurtosis=1.14), with none of this latter group meeting IQ-based criteria for intellectual disability compared with predicted estimates of 2.2%.

Table 6-2 Intelligence classification using WISC-III criteria and comparisons with the theoretical normative curve for the syndromic and nonsyndromic groups

Full Scale Intelligence Quotient	**Classification**	Syndromic (n=13)	Nonsyndromic (n=21)	Total (N=34)	**Theoretical Normal Curve**
		N (% group)		*n (% sample)*	*% population*
110+	High average and above	1 (7.7)	5 (23.8)	6 (17.6)	25.0
90-109	Average	6 (46.2)	14 (66.7)	20 (58.8)	50.0
70-89	Borderline to low average	3 (23.1)	2 (9.5)	5 (14.7)	22.8
<70	Intellectual disability	3 (23.1)	-	3 (8.8)	2.2

6.2.5 Diagnostic Group and subtype comparisons

Table 6.3 shows the breakdown of FSIQ standard scores by diagnostic subtype. Whilst meaningful statistical comparisons between diagnostic subtypes are compromised by extremely sample sizes, these comparisons are frequently reported

on in the psychological literature on this population for samples of comparable size, and thus considered an acceptable form of analysis for the present study findings. Mean global intellectual functioning of the syndromic group was 83.1 (*SD*=21.9), and one standard deviation below the normal population mean, although still within the normal range according to the ICD-10 classification system. Intellectual quotients ranged from 44 to 116, representative of moderate intellectual disability to above average intelligence in this sample. All subjects (n=3) who performed within the intellectually disabled range had syndromic craniosynostosis. Table 6.4 shows the subject diagnostic subtype and age-related characteristics for this subsample.

The NSC subjects displayed global intellectual abilities within normal limits according to ICD-10 criteria (*M*=103.4, *SD*=14.9, range 83 to 143). The distribution of FSIQ scores in this group was positively skewed (skewness statistic =1.06), favouring stronger intellectual performances overall.

Further inspection of the breakdown in mean FSIQ scores by diagnostic subtype (Table 6.4) reveals some variation between the various NSC diagnoses. Whilst small within-group sample sizes caution the interpretability of these findings, multisutural and metopic synostosis was represented by above average mean FSIQ scores. In contrast, the mean FSIQ of sagittal, lambdoid and unicoronal synostoses fell within the average range.

Table 6-3 Descriptive statistics of full scale intelligence quotients by diagnostic subtype in the syndromic and nonsyndromic groups

Diagnosis	**Full Scale Intelligence Quotient**		
	Mean	*SD*	*Range*
Syndromic Craniosynostosis			
Apert syndrome (n=3)	70.0	25.1	44-94
Crouzon syndrome (n=3)	92.3	27.6	62-116
Saethre-Chotzen syndrome (n=5)	85.8	21.9	49-104
Pfeiffer syndrome (n=1)	71	-	-
Witkop Syndrome (n=1)	93	-	-
Nonsyndromic Craniosynostosis			
Unicoronal (n=6)	104.3	14.7	84-124
Sagittal (n=6)	99.5	15.0	83-127
Metopic (n =3)	110.3	4.2	107-115
Lambdoid (n=3)	95.7	2.3	93-97
Multisutural NSC (n=3)	110.0	28.6	93-143
TOTAL	95.6	20.2	44-143

Table 6-4 Full Scale Intellectual quotient (FSIQ) and demographic characteristics of subjects classified within the range of intellectually disability

Syndromic Craniosynostosis Diagnosis	**FSIQ**	**Age**	**Gender**
Apert syndrome	44	7	Female
Saethre-Chotzen	49	12	Female
Crouzon syndrome	62	13	Male

6.3 Information Processing, Learning and Memory, Attention and Executive Functioning

Descriptive statistics were employed to describe the means, standard deviations and ranges of scores for the diagnostic groups on variables assessing information processing, memory and learning, attention and executive cognitive processes. Tables 6.5 and 6.6 present descriptive statistics for measures of information processing, memory and learning, and attention and executive functioning, respectively. Univariate and multivariate ANOVA procedures were performed to test group differences on these variables of interest. As the general intellectual abilities (FSIQ) of the diagnostic groups were shown to significantly differ, and this facet of cognition contributes to the expression of other cognitive functions, FSIQ was entered as a covariate into univariate and multivariate ANOVA's. Results of evaluation of the assumptions of normality of sampling distributions, linearity, homogeneity of variance, homogeneity of regression and reliability of covariates were satisfactory.

6.3.1 Information Processing

Two measures of information processing; the capacity to register information from the environment in auditory-verbal (Digit span) and visuospatial (Block Span) formats were compared. Results of MANOVA with block span and digit span entered as dependent variables, diagnostic group (SC, NSC) as the independent variable and FSIQ as a covariate revealed no significant group differences (*Wilks'* λ =.805, $F(2,22)=2.66$, $p=.093$).

6.3.2 Learning and Memory

Auditory-verbal learning and recall was assessed on the Word Lists and Story Recall test. Word Lists assesses list-learning ability over repeated trials. Story Recall assesses short-term memory for meaningful information in the form of a single presentation of two short stories. Delayed recall tasks for each of these tests measures subjects' long-term retention of learnt material. The Dot Locations task provided a measure of visual learning capacity over repeated trials (DL learning), and retention of information following interference and time delay (DL delayed recall).

A 1 x 6 between-subjects multivariate analysis of covariance examined group differences in visual and verbal memory and new learning. The independent variable was diagnostic group (SC, NSC); FSIQ was the covariate. Two visual memory variables (Dot locations learning score, Dot locations delayed recall) and four verbal learning and memory variables (word lists learning score, word lists delayed recall score, story recall- immediate recall, story recall-delayed recall) comprised the six DV's. No significant main effect for diagnostic group was found for this model, (*Wilks'* λ=.867, $F(6,21)$=.538, p=.774). Descriptive statistics, *F*-statistics and alpha values for these comparisons have been presented in Table 6.5.

6.3.3 Attention and Executive Functioning

Of particular interest to this study are the facets of cognition related to attention and executive functions, which are governed by the frontal lobe regions of the brain. Frontal lobe systems are frequently affected by early brain damage or disease, such as may occur with the pathological processes of craniosynostosis. As such, measures purporting to evaluate these skills have been examined together.

Two facets of attention were examined. The Sky Search Attention score provides a measure of selective attention. Sky Search DT provides an evaluation of sustained-divided attention. Four variables measuring various facets of executive functioning were examined. The Tower of London Test (TOL) Summary score provides a measure of general planning and problem-solving skills. The Verbal Fluency task taps capacity to generate verbal ideas according to an abstract concept or principle. The Complex Figure of Rey Test (CFRT) measures visuospatial construction ability, planning and organisational skill. Scores for accuracy of the reproduction (CFRT Accuracy) as well as ratings of organisational skill (CFRT Organisation) have been examined.

Multivariate analysis of covariance (MANCOVA) tested group differences on the combined dependent variables (TEA-Ch Attention score, TEA-Ch Dual task score, TOL summary score, CFRT Accuracy, CFRT Organisation, and Verbal Fluency). Diagnostic group (SC, NSC) formed the independent variable and FSIQ the covariate. The result of MANCOVA indicated no significant group differences in the combined DV's, (*Wilks'* λ=.813, $F(6,21)$=.804, p=.578). Descriptive statistics,

F-statistics and alpha values for these comparisons have been presented in Table 6.6.

The general findings to emerge from the MANCOVA analyses described above were that, despite the weaker overall intellectual capabilities of the SC subjects, expected group differences on measures of memory and new learning, attention and executive functioning between SC and NSC subjects were not found. Also observed was a trend toward similarly below average performances in both groups on several of the cognitive areas assessed beyond global intellectual functioning, particularly on variables assessing attention and executive abilities.

To further investigate these trends, one-sample t-tests were employed to compare the composite groups' z-score means and the normal population mean of zero on the dependent variables of interest. A Bonferroni-type adjustment was made for inflated Type I error. Results have been presented in Tables 6.7 (Memory and Learning) and 6.8 (Attention and Executive Functioning).

Table 6-5 Descriptive statistics and MANCOVA analyses on memory and learning variables for the syndromic and nonsyndromic groups

	Syndromic (n=10)		**Nonsyndromic (n=19)**		**MANCOVA**	
	Mean	*SD*	*Mean*	*SD*	*F*	*p*
Visual Memory						
DL Learning	-.37	.78	.04	1.01	.37	.55
DL Delay Recall	.33	.70	.58	.78	.25	.63
Verbal memory						
WL Learning	-.03	1.11	.21	.85	.38	.54
WL Delay Recall	.00	1.10	.21	1.25	1.28	.27
SR Immediate Recall	-1.28	1.03	-.62	.89	.49	.49
SR Delay Recall	-1.12	.85	-.67	1.04	.04	.85

WL= Word lists; DL= Dot Locations; SR=Story Recall
MANCOVA; $F(6,21)=.538$, $p=.774$
*$p<.05$

Table 6-6 Descriptive statistics and MANCOVA analyses on attention and executive functioning variables for the syndromic and nonsyndromic groups

	Syndromic (n=11)		**Nonsyndromic (n=18)**		**MANCOVA**	
	Mean	*SD*	*Mean*	*SD*	*F*	*P*
Attention						
TEA-Ch Attention	.00	1.80	.02	.99	1.42	.24
TEA-Ch Dual task	-1.91	1.01	-1.41	1.13	1.20	.28
Executive Functioning						
TOL Summary score	.1.47	1.03	-.58	1.01	1.64	.21
CFRT Accuracy	-1.80	2.00	-1.10	1.30	.003	.96
CFRT Organisation	.57	2.18	1.45	1.39	.03	.87
VFT Total words	-.80	1.39	.12	1.17	.05	.83

VFT= Verbal Fluency Test; TOL= Tower of London Test; CFRT= Complex Figure of Rey Test
MANCOVA; $F(6,21)=.804$, $p=.578$.
*$p<.05$

Table 6-7 z-score differences from normal distribution mean of zero in the syndromic and nonsyndromic groups on memory and learning variables

	Composite Group (N=34)				
Test	Mean difference	95% CI	*t*	df	*P*
Visual Memory					
DL: Learning score	-0.1	(-0.5,0.2)	-0.79	33	.434
DL: Delayed recall	0.4	(0.1,0.7)	2.85	33	.008*
Verbal Memory					
WL: Learning	-0.2	(-0.6,0.2)	-0.86	33	.397
WL: Delayed Recall	0.0	(-0.4,0.5)	.093	33	.927
SR: Immediate recall	-0.9	(-1.3,-0.5)	-4.91	28	.000*
SR: Delayed recall	-0.9	(-1.3,-0.5)	-4.89	29	.000*

WL= Word lists; DL= Dot Locations; SR=Story Recall
*$p \leq 008$

Inspection of the data on memory and new learning variables reveals a trend for both SC and NSC groups to display significantly different immediate auditory-verbal memory abilities from the normal population mean on the Story Recall test (Immediate Recall) and long-term retention component of this task (Delayed Recall).

Table 6-8 z-score differences from normal distribution mean of zero in the syndromic and nonsyndromic groups on attention and executive functioning variables

	Composite Group (N=34)				
Test	Mean difference	95% CI	*t*	df	*p*
Attention					
TEA-Ch: Attention Score	.02	(-0.4,0.5)	0.13	33	.892
TEA-Ch: Dual task score	-1.6	(-2.0,-1.2)	-8.690	31	.000*
Executive Functioning					
TOL: Summary score	-1.0	(-1.4,-0.6)	-5.064	30	.000*
CFRT: Accuracy score	-1.2	(-1.8,-0.7)	-4.680	33	.000*
CFRT: Organisation score	1.1	(0.5,1.6)	3.769	33	.001*
VFT: Total words	-0.2	(-0.7,0.2)	-1.037	33	.307

TEA-Ch= Test of Everyday Attention for Children; VFT= Verbal Fluency Test; CFRT= Complex Figure of Rey Test; TOL= Tower of London Test

*$p \leq 008$

Results of independent t-tests revealed that both the SC and NSC groups performed significantly below the normal population mean on measures of sustained-divided attention (TEA-Ch Dual task), visual-spatial planning (CFRT Accuracy) ability and planning and problem-solving skills (TOL: Summary score). As a group, subjects performed significantly better than the normal population average in visual-spatial organisational skill. Mean differences, confidence intervals and t-test findings have been presented in Table 6.8.

6.4 Reading Ability

There was no significant difference in mean word reading skills of children with syndromic (M=90.5, SD=20.7) and nonsyndromic (M=101.3, SD=16.1) craniosynostosis, $F(1,32)=2.95$, p=.096. Both groups displayed word reading skills at an average standard. One-sample t-tests were employed to compare each diagnostic group with the normal population mean of 100. Results revealed that

neither the syndromic craniosynostosis group (*M*=-.64, SD=*1.38), t*(12)=-1.66, p=1.22) or the nonsyndromic craniosynostosis group (M=-.64, SD=*1.38), t(12)*=0.-1.66, p=1.22) differed significantly in reading ability compared with normative population averages.

6.5 Psychological Functioning

6.5.1 Parent-rated Problem Behaviour Frequencies

Table 6.9 displays descriptive statistics (mean T-scores and standard deviations) and the relative frequency of Problem scores within the Clinical Range (> 95th percentile) for the overall sample. A MANOVA with Internalising and Externalising Problem scores comprising the dependent variables, and diagnostic group (SC, NSC) entered as the independent variable, revealed no significant group differences in total Internalising and Externalising behaviours (*Wilks'* λ=.961, *F*(2,31)=.633,*p*=.54) based on parent ratings. A univariate ANOVA with Total Problem score forming the dependent variable and diagnostic group as the independent variable showed no significant group differences in Total Problem scores (*F*(1,32)=.76,*p*=.40). These results suggest that children with SC and NSC did not significantly differ in internalising or externalising problem behaviors, with both groups functioning within the non-clinical range overall. Internalising problem behaviours of at least Borderline clinical significance were reported more frequently in the overall sample (14.7%, n=5) than Externalising problems (5.9%, n=2).

6.5.2 Teacher-rated Problem Behaviour Frequencies

The same analytic procedures were performed on the Teacher Report Form data as for the CBCL data. Table 6.10 shows the mean T-scores, standard deviations, and the relative frequency of clinically significant teacher-rated Problem scores for children with syndromic and nonsyndromic craniosynostosis. A univariate ANOVA procedure, with Total Problem score as the dependent variable and diagnostic group as the independent variable revealed no significant differences on Total Problems behavioural functioning between diagnostic groups (*F*(1,27)=.13,*p*=.72). A MANOVA procedure on the dependent variables (Internalizing and Externalizing Problem scores), with diagnostic group forming the

independent variable (SC, NSC) similarly showed no significant group differences in Internalizing and Externalising behaviours (*Wilks'* λ =.943,$F(2,26)$=.779,p=.47). Mean T -scores on all the Syndrome and Problem scores fell within the non-clinical range for each diagnostic group. Two children presented with Internalising problems at a clinical level, whilst one child revealed clinically significant Externalising problem. Internalising problems of at least Borderline clinical significance were reported more frequently (20.7%, n=6) than Externalising problems (17.2%, n=5) in the overall sample.

6.6 Gender Comparisons on Psychological Functioning

6.6.1 Parent-rated Problem Behaviour Frequencies

Univariate ANOVA with Total Problem T-score comprising the dependent variable and gender as the independent variable, showed no gender differences in parent-rated Total Problem behaviours for males (mean T-score=49.5, *SD*=11.7) and females (mean T-score=51.3, *SD*=6.7), $F(1,32)$=.28, p=.60). A MANOVA analysis with Internalising and Externalising Problem T-scores entered as the dependent variables, and gender as the independent variable, revealed no significant differences between males and females in parent-rated internalizing and externalising problem behaviours (*Wilks* λ=.91, $F(2,31)$=1.58, p=.22).

6.6.2 Teacher-rated Problem Behaviour Frequencies

Univariate ANOVA with Total Problem T-score comprising the dependent variable and gender as the independent variable, showed no gender differences in teacher-rated Total Problem behaviours for males (mean T-score=50.7, *SD*=9.9) and females (mean T-score=51.4, SD=9.9), $F(1,27)$=.03, p=.87). A MANOVA analysis with Internalising and Externalising Problem T-scores entered as the dependent variables, and gender as the independent variable, revealed no significant differences between males and females in teacher-rated internalizing and externalising problem behaviours, *Wilks* λ=.83, $F(2,26)$=2.72, p=.09) in this sample.

Table 6-9 Descriptive statistics for the syndromic and nonsyndromic groups on parent-rated psychological adjustment variables on the Child Behavior Checklist

Child Behavior Checklist Domain (Parent Report Form)	**Syndromic (n=14)**	**Nonsyndromic (n=20)**	**% Sample in clinical range**
	Mean (*SD*)		
Internalising Score	51.4 (10.6)	48.5 (9.7)	5.9
Somatic Complaints	55.4 (6.2)	56.1 (8.2)	
Withdrawn	57.2 (9.6)	52.1 (3.7)	
Anxious Depressed	52.6 (4.5)	52.5 (4.4)	
Social Problems	57.5 (7.9)	53.9 (6.3)	
Thought Problems	56.7 (8.1)	52.9 (5.9)	
Attention Problems	58.4 (7.2)	53.7 (5.3)	
Externalising Score	47.1 (10.9)	47.8 (10.6)	5.9
Delinquent Behaviour	52.9 (5.2)	53.8 (6.7)	
Aggressive Behaviour	52.8 (4.0)	53.2 (7.2)	
Total Problems (Composite)	52.1 (9.6)	49.1 (9.9)	5.9

Table 6-10 Descriptive statistics for the syndromic and nonsyndromic groups on teacher-rated psychological adjustment variables on the Child Behavior Checklist

Child Behavior Checklist Domain (Teacher Report Form)	**Syndromic (n=12)**	**Nonsyndromic (n=17)**	**% Sample in clinical range**
	Mean (*SD*)		
Internalising Score	48.3 (8.7)	51.9 (12.1)	6.9
Somatic Complaints	52.1 (3.1)	53.6 (6.5)	
Withdrawn	51.8 (4.5)	56.8 (8.9)	
Anxious Depressed	53.5 (5.2)	55.3 (7.7)	
Social Problems	56.6 (6.7)	56.2 (8.6)	
Thought Problems	52.3 (8.1)	52.9 (7.0)	
Attention Problems	54.3 (5.6)	54.6 (5.4)	
Externalising Score	47.7 (6.0)	51.5 (9.8)	6.9
Delinquent Behaviour	50.7 (1.6)	54.9 (7.7)	
Aggressive Behaviour	51.8 (2.9)	54.8 (5.4)	
Total Problems (Composite)	50.3 (6.8)	51.6 (11.5)	6.9

6.7 Case Studies

The group results presented above revealed several trends in the craniosynostosis sample. Perhaps the most outstanding of these was, that despite the significantly higher intellectual abilities of the nonsyndromic group compared to the syndromic group, subjects lacked the expected group differences in more specific areas of cognitive ability, particularly attention and executive skills. Also observed was the wide variability in cognitive functions; both within and between diagnostic conditions. As such, to more accurately represent these trends, single case studies have been presented providing information about the history and performances on neuropsychological testing of these subjects.

6.7.1 Case Study 1: AB

Diagnosis: **Apert syndrome**

Age: **14 years, 1 month**

6.7.1.1 Background History

AB was born via normal vaginal delivery to a 34 year old mother and 28 year old father. Some of the principal features of his diagnosis of Apert syndrome included bilateral choanal stenosis (requiring the insertion of nasal tubes until seven months of age), severe craniosynostosis, a soft palate cleft, and severe syndactyly of both hands and feet.

A CT head scan at six months of age revealed bicoronal synostosis, with a shallow anterior cranial fossae and orbits as well as mild dilatation of the frontal and temporal horns of the lateral ventricles. AB underwent major craniofacial surgery (coronal synostosis craniectomy and bilateral fronto-orbital advancement) at six months of age to improve his skull shape and brain growth potential. He also had numerous other surgical procedures over the years for his condition, including cleft palate repair (2 years of age), and multiple hand and foot surgeries for improvement of limb function, as well as midface advancement surgery at 11 years of age.

His other relevant medical history included an apnoeic episode when less than one month old, requiring resuscitation. There was no information as to whether AB

suffered hypoxia as a result of this episode, but he reportedly remained floppy and lethargic for 15-30 minutes thereafter.

A medical review when AB was three years of age revealed developmental delays; he was not walking alone and his speech consisted of single words only at that time. He was also diagnosed with mild to moderate hearing loss at three years of age. He had tubes inserted at 3 years of age and wore hearing aides for periods over the years.

In terms of his educational history, whilst considered a bright boy, AB's primary school years were apparently marked by some conflict with teachers around his behaviour. He continued to receive integration aide assistance for the majority of his school week (4/5 days) upon his commencement at a mainstream secondary school. Whilst considered to be a capable student academically, the main concerns raised about AB's cognitive abilities related to poor organisational skills and self-regulation of social behaviour.

Table 6-11 Case study AB: Neuropsychological assessment results

Neuropsychological Domain	**Standard Score (SS)**
Intellectual Quotient (IQ)	*SS (mean=100; SD=±15)*
Full Scale IQ	94
Verbal IQ	92
Performance IQ	98
Memory and New Learning	*SS (mean=0, SD=±1)*
Visual	
Dot Locations Learning	0.0
DL Delay Recall	-1.3*
Verbal	
Word Lists Learning	0.7
Word Lists Delay Recall	0.0
Stories Immediate Recall	-0.3
Stories Delay Recall	-0.8
Attention	
TEA-Ch Attention score	0.0

TEA-Ch Dual Task	-1.3*
Executive Functioning	
Verbal Fluency-total words	-0.1
CFRT Accuracy score	-6.1**
CFRT Organisation score	-0.2
TOL Summary score	-1.4*
Academic	
Reading	0.6

* *≥1 SD below mean;* ** *≥2 SD below mean*

AB's global intellectual abilities were within the average range according to WISC-III criteria, with little difference between verbal and visual-spatial abilities. This performance placed him within the normal range of intelligence according to ICD-10 diagnostic criteria. Other results revealed age-appropriate capacity to learn verbal and visual material that was repeated. His retention of visual material after a long delay was found to be impaired due to qualitative features of impulsivity. Verbal memory skills were relatively weaker for more complex material that was delivered via a single presentation. Reading abilities were within age-appropriate limits and consistent with his level of intellectual capability.

Despite his 'average' intelligence, AB's cognitive profile revealed below average performances in attention and executive functioning. Hence, whilst able to sustain attentional focus under simple task demands, he had difficulty with a more complex task of divided attention (TEA-Ch Dual task). He displayed significant difficulties with the executive aspects of visual-spatial planning (CFRT Accuracy). Similarly, his performance on the TOL task reflected impairments with forward planning and self-regulatory mechanisms. Verbal memory weaknesses (Stories task) reflected executive cognitive deficits which influenced the planning and organization of material for memory formation.

Behavioural features of his performances supported quantitative assessment findings. AB was observed to be impulsive in his responses and approach to tasks, and benefited from the provision of task structure.

6.7.2 Case Study 2: CD

Diagnosis: **Saethre-Chotzen syndrome**

Age: **8 years, 6 months**

6.7.2.1 Background History

CD was born at term via emergency caesarean section due to foetal distress, following an uncomplicated pregnancy.

CD showed many of the classic features of Saethre-Chotzen. He had mild hypertelorism and syndactyly of the second web space in his hands, shallow orbits, bilateral ptosis and, on CT scan, bilateral coronal synostosis and frontosphenoidal synostosis with a shallow anterior cranial fossae. He underwent a bifronto-orbital advancement at seven months of age to correct his skull deformity. He later underwent surgery to correct right-sided strabismus and upper eyelid ptosis at 3 years of age.

CT skull at 5 years of age revealed extensive vault craniosynostosis and prominence of the convolutional markings, but no intracranial abnormalities. A subsequent CT skull at 6 years 9 months showed a microcephalic and brachiocephalic skull and absence of frontal sinuses. Several skull vault defects were noted in the frontal region, with the largest of these in the left frontal region, where they measured up to 3cm in diameter. No intracranial abnormalities were however identified at this time. Raised intracranial pressure was detected at age 6½ years, following insertion of an ICP monitor. CD underwent another bifronto-orbital advancement surgery at 7 years of age to redo the earlier surgery and increase cranial vault capacity.

CD presented with a family history of Saethre-Chotzen, affecting his mother and two distant cousins (2^{nd} and 3^{rd} cousins). A cousin, unaffected by Saethre-Chotzen, was also reportedly diagnosed with Attention Deficit Disorder.

His other medical history includes a diagnosis of bilateral conductive hearing loss at 10 months of age. He also experienced recurrent episodes of bilateral otitis media with effusion, requiring insertion of grommets (tubes) in both ears on multiple occasions. CD was fitted with a hearing aid for use in classroom activities, although parental reports suggest that this was not used on a routine basis. The timing of CD's early motor and language developmental milestones were not accurately recalled, but believed to have been within normal limits.

CD was attending Grade 3 year at a mainstream primary school when seen for the assessment. Parental reports suggested that he was making satisfactory academic progress, although showed minor weaknesses with respect to handwriting skills.

Table 6-12 Case study CD: Neuropsychological assessment results

Neuropsychological Domain	**Standard Scores**
Intellectual Quotient (IQ)	*SS (mean=100; SD=±15)*
Full Scale IQ	99
Verbal IQ	98
Performance IQ	100
Memory and New Learning	*SS (mean=0, SD=±1)*
Visual	
Dot Locations Learning	-0.7
DL Delay Recall	0.0
Verbal	
Word Lists Learning	0.7
Word Lists Delay Recall	0.0
Story Immediate Recall	-0.3
Story Delay Recall	0.3
Attention	
TEA-Ch Attention score	0.0
TEA-Ch Dual task	-2.0**
Executive Functioning	
Verbal Fluency-total words	-1.4*
CFRT Accuracy score	-1.6*
CFRT Organisation score	1.2
TOL Summary score	Missing
Academic	
Reading	0.1

** ≥1 SD below mean; ** ≥2 SD below mean*

CD's global intellectual abilities were within the average range, with comparable verbal and visual-spatial thinking abilities, and consistent with a diagnostic classification of normal intelligence according to ICD-10 diagnostic criteria. Other results indicated age-appropriate learning and retention for verbal and visual material. Reading abilities were within age-appropriate limits and consistent with his intellectual capabilities.

Despite performing within the average range of intelligence, CD's cognitive profile was marked by below-average performances on attention and executive skills. Whilst able to sustain attentional focus under simple task demands, he showed moderately severe deficits with sustained-divided attention. His difficulties may in part, be attributable to his hearing difficulties, since this task involved delivery of material via auditory and visual modalities. Verbal fluency, associated with the capacity to spontaneously generate verbal ideas whilst adhering to a specific rule or principle was also below average.

6.7.3 Case Study 3: EF

Diagnosis: **Unilateral coronal synostosis (right-sided)**

Age: **7 years, 3 months**

6.7.3.1 Background History

There was no reported family history of craniosynostosis for EF. The pregnancy with EF was reportedly normal, although her mother had elevated blood pressure in the final weeks. EF was born to term by forceps delivery. A CT skull shortly after her birth confirmed a diagnosis of right coronal synostosis. No intracranial abnormality was reported at that time. EF underwent fronto-orbital advancement surgery at eight months of age to correct her skull deformity.

EF reportedly made normal gains with motor and language developmental milestones in her early years. There was no reported history of hearing or vision difficulties. She was completing her Grade 2 year when she participated in the study, where her reported strengths were in her general intellectual skills. Parent/ school reports indicated That EF had, however, made slow progress with reading and she had a brief period of remedial intervention in mathematics. Minor attentional difficulties were also noted.

Table 6-13 Case study EF: Neuropsychological assessment results

Neuropsychological Domain	Standard Scores
Intellectual Quotient (IQ)	*SS (mean=100; SD=±15)*
Full Scale IQ	124
Verbal IQ	110
Performance IQ	136
Memory and New Learning	*SS (mean=0, SD=±1)*
Visual	
Dot Locations Learning	0.0
DL Delay Recall	0.3
Verbal	
Word Lists Learning	0.7
Word Lists Delay Recall	2.3
Story Immediate Recall	0.5
Story Delay Recall	-0.2
Attention	
TEA-Ch Attention score	-1.0*
TEA-Ch Dual Task	-3.0**
Executive Functioning	
Verbal Fluency-total words	0.3
CFRT Accuracy score	-1.2*
CFRT Organisation score	0.5
TOL Summary score	-2.2**
Academic	
Reading (WRAT-3)	0.3

* *≥1 SD below mean;* ** *≥2 SD below mean*

EF's global intellectual abilities were within the 'superior' range overall, but marked by significant variability between visual and verbal abilities, a discrepancy which occurs in less than 4% of the age-matched normal population. The

variability in her verbal skills related to immediate auditory verbal memory span and mental arithmetic skills, which were relatively weaker than her other verbal skills. Visual-spatial (nonverbal) thinking abilities were of an at least high average standard.

On the other cognitive domains assessed, EF showed satisfactory learning and retention of verbal and visual material that was repeated. Her overall performance on these tasks was, however, below that expected of her above average intellectual capabilities. Similarly, whilst at an age-appropriate level, EF's reading and arithmetic skills (WISC-III Arithmetic subtest, scaled score=9) were below that expected in the context of her intellectual capabilities.

EF's cognitive profile revealed mild to moderately severe neuropsychological deficits in several areas assessed, particularly with respect to attention and executive cognitive skills. Her cognitive profile was marked by average to well-below average performances in these areas, which is out of keeping with her above average intellectual skills. Hence, she struggled to focus attentional resources at a simple level, with her performance declining further under more complex attentional demands. Her capacity for forward planning and self-regulation of her responses and behaviour was impaired; these deficits being particularly noticeable on unstructured tasks where she was required to formulate her own approach. Qualitative features of her test performance reflected formal test results; she was highly self-distractible, and required external structure and prompts as she proceeded with tasks, particularly on those of a novel nature. Without such support, she had difficulties self-regulating her responses and actions.

6.7.4 Case Study 4: GH

Diagnosis: **Nonsyndromic multiple suture synostosis**

Age: **9 years, 1 month**

6.7.4.1 Background History

GH was born to term after a normal pregnancy and birth. There was no prior family history of craniosynostosis or other related conditions. A CT skull scan following birth indicated fusion of both coronal sutures and the sphenofrontal suture, and broad and relatively shallow anterior cranial fossae. A mild prominence of the temporal horn of the right lateral ventricle was reported, but no temporal lobe

atrophy was indicated. The brain parenchyma was reportedly normal. There was no reported family history of craniosynostosis or other related conditions.

Developmental milestones appeared to have been met within normal limits. There was no reported history of hearing or vision difficulties.

GH was attending Grade 3 at his local primary school at the time of his participation in the study, where he was reportedly making age-appropriate progress in many academic areas, in the context of mild weaknesses in writing, English and Arithmetic. His parents also acknowledged mild difficulties with attention, planning and organizational skills for GH.

Table 6-14 Case study GH: Neuropsychological assessment results

Neuropsychological Domain	**Standard Scores**
Intellectual Quotient (IQ)	*SS (mean=100; SD=±15)*
Full Scale IQ	94
Verbal IQ	100
Performance IQ	89
Memory and New Learning	*SS (mean=0, SD=±1)*
Visual	
Dot Locations Learning	-1.7*
DL Delay Recall	-0.7
Verbal	
Word Lists Learning	0.0
Word Lists Delay Recall	-1.7*
Story Immediate Recall	-0.5
Story Delay Recall	-0.7
Attention	
TEA-Ch Attention score	-0.7
TEA-Ch Dual Task	-3.0**
Executive Functioning	
Verbal Fluency-total words	0.3
CFRT Accuracy score	-2.4**

CFRT Organisation score	1.1
TOL Summary score	-0.8
Academic	
Reading	0.1

**>1 SD below mean; **>2 SD below mean*

GH's global intellectual abilities fell within the average range, associated with significantly stronger verbal than visual-spatial abilities. This performance placed him within the normal range of intelligence according to ICD-10 diagnostic criteria. Reading abilities were within the average range and consistent with GH's intellectual capabilities. Other results revealed a satisfactory learning curve for verbal information that was repeated, although very weak visual learning skills. His retention of both verbal and visual material over time was also impaired.

GH's cognitive profile also revealed impairments in attention and executive cognitive functions. Whilst able to sustain focus under simple attentional demands (TEA-Ch Attention) he displayed significant weakness on a more complex task of sustained-divided attention (TEA-Ch Dual Task). He also displayed planning and organisational weaknesses, which affected his capacity to impose his own structure to tasks and self-regulate his performance.

GH's profile revealed a number of features. Firstly, despite average intellectual abilities, he displayed many below-average performances in the areas of attention and executive functioning. Furthermore, he displayed memory and new learning deficits affecting both verbal and visual material. In this regard, a CT scan at 4 months of age showed mild prominence of the temporal horn of the right lateral ventricle, but no temporal lobe atrophy. Review CT scan at the time of the assessment would have been helpful in elucidating whether there had been any structural brain changes over time that may have produced the pattern of cognitive deficits seen on assessment, since his pattern of test scores would be consistent with temporal lobe dysfunction.

6.7.5 Summary and Formulation

The following themes emerged from the above cases reviewed:

All subjects displayed at least average intellectual abilities. Despite this, their cognitive profiles were consistently characterised by mild to moderately severe neuropsychological dysfunction, with the main deficits being with attention and executive cognitive skills. These deficits were unrelated to general intellectual abilities. The nature of the neuropsychological deficits identified in these cases, namely associated with attention and executive functions, are subsumed within the frontal lobe brain regions, and considered the most susceptible of cognitive skills to the effects of early brain injury. The underlying causative factors for these difficulties will be reviewed in the following discussion chapter.

Chapter Seven

7 Discussion

The issue of the functional repercussions of craniosynostosis presents a fundamental question: Do these conditions produce organic impairment, and, if so, how is this functionally manifest at a cognitive level? Do the neuropsychological profiles of the syndromic and nonsyndromic craniosynostoses differ? What are the developmental implications for children affected by this disorder?

The neuropsychological literature on the craniosynostoses is marked by two main areas of limitation. Firstly, the long term cognitive characteristics of these conditions are poorly understood, with the majority of psychometric studies focusing on the infancy and preschool years, and centering on the merits and timing of surgical intervention. Secondly, there is a paucity of literature that has empirically examined the full range of cognitive functions in the craniosynostoses, beyond the simple assessment of global intelligence. The few published neuropsychological studies (e.g. Magge et al., 2002; Turtas et al., 1993) have not included comprehensive assessments of all key cognitive domains in the reported protocols. Hence, cognitive processes which develop and mature throughout childhood and adolescence, such as information processing, memory and new learning and higher-order abilities (e.g. attention and executive functioning), have not previously been quantified using objective assessment measures in the same sample of children.

The objective of the present study was to address some of these limitations and provide a detailed characterisation of the neuropsychological profiles of children and adolescents with craniofacial anomalies. The chosen study population was older than that of many previous studies (age range 7 to 16 years), so that more specialized cognitive skills could be evaluated with greater precision.

Based on the empirical literature and clinical experience, it was predicted that children with syndromic craniosynostosis would display lower intelligence than children with nonsyndromic craniosynostosis and the normative population. It was also predicted that the general intellectual abilities of children with nonsyndromic craniosynostosis would not significantly differ from normative population

estimates. Children with syndromic craniosynostosis were also predicted to perform significantly below normative population rates in the specific cognitive domains of information processing, attention, executive functioning and memory and learning. On the basis of the developmental neuropsychological literature, it was speculated that children with nonsyndromic craniosynostosis would also differ significantly from normative population averages in these more specialized cognitive domains.

7.1 Intellectual Outcomes

Consistent with predictions, children with syndromic craniosynostosis in the present sample displayed significantly lower mean general intellectual abilities (Full Scale Intellectual quotient; IQ=83) than that of the normal population (mean IQ=100) and the study's sample of children with nonsyndromic craniosynostosis (mean IQ=103). Interestingly, however, whilst the syndromic craniosynostosis group were represented by a higher prevalence of intellectual disability (23%) than predicted population rates (2.2%), 77% of these individuals were of normal intelligence, and 46% percent were of average or above average intelligence (IQ ≥ 90). These findings hence promisingly challenge the clinical impression of some authors (e.g. M. M. Cohen & Kreiborg, 1990; Elia et al., 1996) that intellectual disability is an essential feature of these conditions.

With respect to the specific syndromes, children with Apert syndrome were represented by the lowest intelligence (mean IQ=70; range 44-94). These findings are congruent with the majority of psychometric literature in showing a variable pattern of intellect in Apert syndrome which ranges from mental retardation to normal intelligence, although appearing typically skewed towards the lower end of the intellectual spectrum (e.g. Lajeunie et al., 1999; Lefebvre et al., 1986; Patton et al., 1988; Renier et al., 1996; Sarimski, 1997; Renier et al., 2000), Whilst one study (Shipster, Hearst, Dockrell et al., 2003a) described better intellectual outcomes in children with Apert syndrome than found in this and prior studies, their sample comprised children of a young age (4 to 5 years). It is possible that assessment of these children as they mature may yield a more variable developmental pattern of intellectual ability.

With respect to the other syndromic conditions in this study, the mean IQ of the various diagnostic subtypes fell within normal limits, although as with Apert

syndrome, wide variability, from moderate intellectual disability to high average intelligence, characterised this sample. Comparisons with other studies are limited by the lack of published psychometric data available on the syndromic craniosynostoses. Of those available, Noetzel et al., (1985) reported on 23 children with syndromic craniosynostosis (Apert, Crouzon, Pfeiffer and Saethre-Chotzen syndrome). Sixteen out of 23 (70%) of their combined sample achieved IQ scores above 90, which is higher than that of the current sample (54%). Differences between the results of Noetzel et al., (1985) and the present study findings may be attributable to the variation in ages tested to some extent; 70% of their sample were below 2 years of age, compared to the present sample of children of whom the mean age was 11 years. The interpretability of the findings of Noetzel et al., (1985) is also questionable due to the wide age range included in the same sample (age 2 months to 21 years) since there is a danger that collapsing results for children of widely different ages will obscure differences in cognitive profiles over time. This also limits meaningful comparisons across studies. Of note, one child in the present syndromic craniosynostosis sample had a rare disorder, Witkop syndrome. An extensive review of the literature did not yield published psychometric studies on children, and thus the intellectual profile of this subject (IQ=93) appears one of the first reported in the literature.

Children with nonsyndromic craniosynostosis in this study were all of normal intelligence (IQ>70), displaying mean intellectual abilities within the average range (103.4; *SD*=14.9). In addition, higher than predicted proportions (91.5% compared with general population estimates of 75%) were of average intelligence or above (IQ ≥90). Study findings are firstly consistent with existing research showing better intellectual outcomes in nonsyndromic than syndromic craniosynostosis (e.g. Bhardwaj & Rohtagi, 1994; Noetzel et al., 1985). Findings similar to the present study have been documented in previous studies that have measured intelligence in children with sagittal synostosis of comparable ages to the current sample. Magge et al., (2002) reported above average intelligence (mean IQ=110.6) in children aged 6 to 16 years with sagittal synostosis. Shipster and colleagues (Shipster, Hearst, Somerville et al., 2003b) found an increase of high average to exceptionally high intelligence in children aged between 3 and 15 years with this condition. Our findings, of course, need to be viewed with some caution due to the small group of children with nonsyndromic craniosynostosis (n=22), and specifically sagittal

synostosis (n=6). It is indeed possible that a larger sample may have yielded a wider distribution of test scores than that observed.

The present study findings provided no evidence for an increased risk of intellectual deficit based on a particular type of nonsyndromic craniosynostosis. Contrary to theoretical expectations that one might expect a greater risk of brain insult, and secondarily, cognitive deficit in association with more severe anatomic deformities, our multisutural NSC subjects were of high average intelligence (mean IQ=110). Alongside those with metopic synostosis, these subjects showed the highest mean intelligence of their nonsyndromic counterparts. The finding of high average intelligence in metopic synostosis patients stands contrary to studies reporting a high prevalence of developmental delay in this disorder (e.g. Montaut & Stricker, 1977; Sidoti et al., 1996). Chromosomal anomalies and other malformations (e.g. visceral, brain, heart malformations) have been linked with poorer cognitive outcomes in some affected samples (e.g. Lajeunie et al., 1998). However, chromosomal studies were not routinely performed on our study participants, and thus interrelationships with intellectual outcomes cannot be determined.

7.1.1 Age-Based Trends in Intellectual Functioning

Intelligence did not significantly differ between younger (7 to 11 years of age) and older (aged 12 years or more) study participants. This may therefore imply no significant deterioration in intellect over time in children with craniosynostosis, at least in those of school age. However, longitudinal studies which follow the same children over time would be required to verify these findings. Earlier research investigations (e.g. Arnaud et al., 1995) examining long-term outcomes in children with craniosynostosis can be criticized for inferences about developmental functioning based on intellectual assessment findings alone. Developmental neuropsychological literature provides consistent evidence to show that, in the context of brain insult, cognitive profiles can show marked variability, and furthermore that general intelligence alone, may not capture discrepancies in skills which appear more vulnerable to the effects of brain injury. Thus, inferences about the integrity of cognitive processes should be made only in the context of comprehensive assessment of the array of cognitive skills, beyond general intellect, that contribute to overall adaptive functioning.

7.2 Information Processing, Memory and Learning, Attention and Executive Functioning

It was predicted that, commensurate with their lowered general intelligence, children with syndromic craniosynostosis would show impairments in the other cognitive domains assessed; namely information processing, memory and new learning, attention and executive cognitive processes. The present findings did reveal impairments in some, although not all, cognitive domains, with both syndromic and nonsyndromic groups showing age-appropriate performances on some measures of information processing and rote-style anterograde verbal and visual memory. Whilst speculated that children with nonsyndromic craniosynostosis would display deficits on these "non-IQ" cognitive domains, these children also performed to a normal standard on measures of information processing and rote-style anterograde verbal and visual memory.

What did emerge in this sample was evidence of significantly below average performances on measures of attention and executive function in both the syndromic and nonsyndromic groups. Specifically, complex divided attention and planning and problem-solving ability were affected. Consistent with this pattern of executive cognitive dysfunction, deficits on an immediate auditory verbal memory task (Story Recall Task) that placed additional demands on these abilities was also evident in each group. Cognitive deficits in the syndromic craniosynostoses were expected to some extent, since this group was functioning below normative population averages with respect to general intelligence and, in the absence of additional brain trauma, cognitive skills in these more specialised domains are expected to be approximately commensurate with general intelligence. In contrast, the cognitive deficits in the NSC sample could not be explained by general intelligence, since these children were of average ability (mean IQ=103). This data therefore implies firstly, the presence of at least mild organic dysfunction in the craniosynostoses, and secondly, suggests a significant risk of mild neurologic disability in the nonsyndromic craniosynostoses, that may not have previously been recognised.

Learning difficulties, Attention Deficit Hyperactivity Disorder (ADHD) and social and behavioural dysfunction have been reported in samples of school-aged children with nonsyndromic craniosynostosis (Bottero et al., 1998; Kapp-Simon, 1998;

Magge et al., 2002; Rozelle et al., 1995; Sidoti et al., 1996). Problems with attentional control, concentration (Shipster, Hearst, Dockrell et al., 2003a) and hyperactivity (Sarimski, 1997) have similarly been identified in children with syndromic craniosynostosis (Apert syndrome). Attention and executive cognitive deficits have been postulated as an underlying factor in these conditions by some authors (e.g. Speltz et al., 1997; Kapp-Simon, 1998), although not been previously demonstrated using standard assessment instruments that measure these functions. This study is one of the first to provide empirical support for the presence of disturbances in these cognitive domains using standardised assessment measures; findings of which may inform the underlying etiology of these craniofacial disorders.

7.3 Early versus late-operative outcomes and intelligence

The functional cognitive significance of the timing of surgical intervention to correct synostosis has been widely debated in the literature, with psychometric investigations examining this issue by comparing of early and late-operative samples on cognitive variables. In the present study, general intelligence in those undergoing early (< 1 year of age; n=27) versus late (> 1 year of age; n=6) synostosis correction did not significantly differ. Findings may lend support to the notions of some that timing of surgery does not make a significant contribution to intellectual outcomes (Arnaud et al., 1995; Kapp-Simon, 1998; Kapp-Simon et al., 1993; Shipster, Hearst, Somerville et al., 2003b). However, other factors such as number of craniofacial procedures, intra-and post-operative complications, and the small sample size of late-operative patients should be acknowledged when drawing inferences from these results. There may also be a potential selection bias in late-operative patients in this, and previous studies; these individuals may have complex medical problems (e.g. cardiac anomalies) which necessitate the delay of synostosis correction surgery. Such risk factors for cognitive dysfunction may hence be unrelated to the surgical procedure per se.

7.4 Cognitive Diversity in Craniosynostosis- Case Studies

The four case studies presented illustrate the type of cognitive dysfunction that may be manifest in children with craniosynostosis; the nature of which can have a

significant impact on everyday adaptive living skills, including the capacity to meet educational demands.

Case Studies 1 and 2 detailed the neuropsychological profiles of a 14 year old male (AB) and 8 year old male (CD) with Apert syndrome and Saethre-Chotzen syndrome, respectively. AB was of average intelligence (IQ=94), as was CD (IQ=99). Two cases of nonsyndromic craniosynostosis were also presented. Case 3 (EF) described a 7 year old girl with right-sided unicoronal synostosis, and Case 4 (GH), a 9 year old boy with multisutural synostosis. EF was of superior intelligence (IQ=124) and GH was of average intelligence (IQ=94). Common to all these cases was the, at least average, general intelligence. Despite this, these children's cognitive profiles were consistently characterised by mild to moderately severe neuropsychological dysfunction, primarily associated with attention and executive cognitive deficits. Thus, whilst these children differed with respect to diagnosis, a similar pattern of cognitive difficulties, albeit to varying degrees of severity, characterised their neuropsychological profiles. These cases illustrate firstly, that children with different types of craniosynostosis can display a common pattern of neuropsychological deficits which implicates anterior cerebral brain regions. Secondly, the risk of cognitive dysfunction appears to affect a wider range of children with craniosynostosis than previously thought. Neuropsychological dysfunction was identified in children with both syndromic and nonsyndromic craniosynostosis, the nature of which can have significant implications for everyday adaptive functioning, including the capacity to meet educational demands. In addition, these results highlight the variability that may be seen in patient profiles: there was, at times, marked variability in these subjects' cognitive profiles, the nature of which may not necessarily be detectable through intellectual evaluation alone. The aetiology of these disturbances will be discussed in more detail below.

7.5 Aetiology of Cognitive Dysfunction

This study identified attention and executive cognitive dysfunction in school-aged children with syndromic and nonsyndromic craniosynostosis. In elucidating the aetiology of these cognitive deficits, a number of factors are important to consider, which relate to the nature, timing and mechanisms of craniosynostosis.

It is well accepted that skull and brain growth are interdependent. Thus, skull expansion is dependent on the forces of brain growth, and conversely, the brain requires the skull to expand to permit normal growth. The mechanisms of craniosynostosis result in restricted skull growth in a direction perpendicular to the fused suture, and compensatory expansion in a direction parallel to the site of sutural fusion. Therefore the rapidly growing brain is 'forced' to grow away from the fused sutural site due to the restricted capacity of the skull, into areas that can accommodate expansion. In the majority of cases, this process occurs at variable stages inutero. However, treatment via cranial vault expansion occurs postnatally, typically between 9 and 12 months of age. This pattern of restriction and compensatory abnormal expansion, persists for a prolonged period prior to intervention, depending on the timing of sutural fusion. This process can thus interfere with the normal course of central nervous system formation and development during its period of most rapid growth, within the pre- and postnatal period. It is plausible that this process can hence result in cerebral dysfunction via disruption to the normal formation and maturation of the central nervous system during a critical phase of development.

The timing of brain insult has significant implications for the nature and severity of deficits that may ensue. Early brain injury vulnerability proponents postulate that brain insults acquired early in life are particularly detrimental to cognitive development, and, may be more detrimental than later-onset injury (e.g. Hebb, 1949). This is because, as Hebb contended, some aspects of cognitive development are critically dependent on the integrity of specific cerebral structures at particular developmental stages. Hence, damage or loss of function at an early stage of central nervous system development can have implications for the development and performance of later-maturing structures and related cognitive processes. As stated above, the pathological process of craniosynostosis, in the vast majority of cases, occurs at variable times inutero. The developmental neuropsychology literature has identified children incurring lesions within the prenatal period or within the first year of life as particularly vulnerable, as showing the greatest impairment (V. Anderson, 1988; V. Anderson, Bond et al., 1997; Duchowny, 1996) with prenatal injuries associated with the poorest outcomes (Leventer et al., 1999). Brain insult during this elemental phase of development affects an immature central nervous system at a time of its most rapid growth. Any disruptions to the central nervous

system during this period can slow the rate, and lead to deviant patterns of its formation and maturation, with obvious implications for related cognitive processes.

Later-developing cognitive processes, specifically those important to the acquisition of knowledge and skills; learning and executive functions, are considered the most vulnerable to the effects of early brain insult (Ewing-Cobbs et al., 1997; Wrightson et al., 1995). The growth pattern of these abilities is prolonged, improving sequentially throughout childhood, concurrent with growth spurts in frontal lobe development (Levin et al., 1991; Thatcher, 1991, 1992; Welsh & Pennington, 1988). There is a growing body of neuropsychological literature that provides support for the mediation of executive functions, which include attentional skills, via anterior cerebral regions; specifically the prefrontal cortex. Prefrontal brain regions have rich, reciprocal connections with virtually all other parts of the brain (Stuss & Benson, 1987), and are therefore dependent upon the integrity of other cerebral areas for input. It follows that dysfunction of other cerebral regions can have 'secondary' implications for the functional efficiency of frontal brain regions.

This study showed that children and adolescents with craniosynostosis in the present study demonstrated a pattern of cognitive deficits that was indicative of frontal lobe dysfunction. These findings are consistent with the neuropsychological literature with respect to the long-term significance of prenatal brain injury upon the later-maturing anterior brain region cognitive skills. Hence, it may be contended that the process of craniosynostosis interferes with the normal mechanisms of central nervous system formation and maturation during a critical developmental phase, and resulting in dysfunction to brain regions which are most susceptible to such disturbances, namely anterior cerebral regions.

The common feature of all the children in this sample was the presence of craniosynostosis. However, these children also differed with respect to underlying diagnostic subtype, medical problems associated with their conditions (e.g. respiratory disorders, cardiac anomalies, genetic mutations, and brain malformations) that could, alone or in combination, have contributed to cognitive outcomes. As such, it is unrealistic to attempt to isolate the effects of craniosynostosis in isolation upon the cognitive features of these disorders; study

findings must be interpreted in consideration of the range of contributory factors that are known to be influential upon these and other conditions.

The interval between insult and evaluation of outcome, and the age at evaluation are particularly important to consider in interpreting the present study findings. Due to the protracted course of central nervous system maturation, which proceeds throughout childhood and adolescence, the effects of early brain insult may not be realized until a time when related emerging skills become functional, and more readily measurable. Although children may appear seemingly functionally intact post-insult, over time they may fail to make age-appropriate developmental gains (Dennis, 1989, 1999). As a result, the gap between children with brain dysfunction and their peers will widen with time, and, as new skills are expected to develop during later childhood, additional deficits may emerge for the injured child. Interpreted in the context of the disorder of craniosynostosis, the majority of psychometric studies in the nonsyndromic entities (the syndromic craniosynostoses may have additional complicating factors, such as brain anomalies that may produce cognitive deficits from birth) suggest seemingly normal neurodevelopmental functioning in the infancy and early childhood years. It is quite possible that these children demonstrate the emergence of cognitive deficits as cerebral regions mature and become more specialized. Such notions have been increasingly acknowledged by authors who have alluded to the potential risks of subtle cognitive dysfunction in children with nonsyndromic craniosynostosis as they reach school-age (Kapp-Simon et al., 1993; Speltz et al., 1997). Following the present sample of children from an early age may have allowed us to address this issue empirically.

Developmental neuropsychological research has also shown that, due to the protracted nature of CNS development and maturation, as well as the mechanisms of recovery following brain insult, the impact of early disruptions to central nervous system growth and maturation may not be fully evident until later in the developmental course. Hence, whilst the majority of the psychological literature on the craniosynostoses has focused on infant development, it is quite possible that children can display seemingly normal developmental functioning early on, yet cognitive deficits may emerge as they mature. This highlights the importance of future studies that employ longitudinal data collection methods may enable us to more accurately chart the developmental trajectories of these individuals, and

potentially delineate critical periods of vulnerability in craniosynostosis populations.

7.6 Predictors and Correlates of Cognitive Dysfunction

This study shows that neuropsychological dysfunction occurs frequently in the craniosynostoses. Whilst the implications for central nervous system development due to the process of craniosynostosis have as yet not been clearly established, it is probable that multiple and heterogeneous factors influence the cognitive profiles of children with this condition, particularly in the syndromic conditions where craniosynostosis occurs as part of a broader symptom complex.

It may be that the brains of children with craniosynostosis are intrinsically different from their non-afflicted counterparts; factors. For example, defects in the genetic program can result in serious malformations in brain size and structural organisation. As addressed previously, restricted and compensatory growth patterns of the cerebrum as a result of craniosynostosis may alter the course of central nervous system development and maturation in the long-term,

Many of these children present with a variety of other medical findings known to be influential upon cognition. Hence, raised intracranial pressure, hydrocephalus and primary abnormalities of the brain and other organ systems, were reported for a small subgroup of children with syndromic craniosynostosis in the present study. Psychosocial factors (e.g. SES status, family history of intellectual disability and/ or learning difficulties) or indeed other unknown factors, may also be of relevance, although not reported in the histories of subjects in this sample. Chronic or episodic hearing problems at the level of the central nervous system or due to conductive difficulties have been indicated with relative frequency in the craniosynostoses, particularly in the syndromic conditions (e.g. Apert syndrome). Hearing impairments can have adverse effects on expressive and receptive language skills and development (Haggard, Birkin & Pringle, 1993), and subsequent cognitive outcomes. Hearing loss and/ or recurrent middle ear infections were noted for a number of this study's participants and present a worthy area of more detailed examination.

Some authors (e.g. Noetzel et al., 1985) have attributed familial-genetic, brain (hydrocephalus, nonprogressive ventriculomegaly) and congenital anomalies to the

etiology of intellectual dysfunction in Crouzon syndrome. There was no reported family history of intellectual deficits that may have contributed to the intellectual dysfunction in those for whom it was observed in the present sample. Insufficient neuroimaging data was available to explore interrelationships between brain anomalies and intellectual outcomes.

The functional impact of surgical correction for synostosis upon cognition has been widely debated in the literature. Treatment of craniosynostosis requires major cranial vault surgery (fronto-orbital advancement in most cases), which involves manipulation of the cranium and its underlying contents. Such an intervention carries all the inherent risks of craniofacial and neurosurgical procedures. Postoperative complications following cranial vault expansion surgery include development of hydrocephalus and hindbrain herniation (Thompson, Jones, Harkness, Gonsalez, & Hayward, 1997). A high incidence of frontal extradural collections at the site of fronto-orbital advancement in infants and young children with Apert syndrome following successful surgery have also been reported (Moore & Abbott, 1996; Posnick et al., 1994). This treatment also carries the risk of haematomas in regions of intervention, and complications arising from infection.

Furthermore, this procedure occurs at a 'critical' time of rapid brain growth and central nervous system maturation. The functional implication of 'interference' with the brain during this period is an area that has been widely studied in the literature through comparisons of neurodevelopmental functioning in infants pre- and post cranial vault remodeling surgery. Findings to date appear mixed and inconclusive. What cannot be assessed from the current study findings is whether cognitive dysfunction is actually eliminated or minimized through early surgery and, furthermore, whether the risks outweigh the benefits of surgery as this relates to cognitive outcomes.

These issues warrant further investigation, ideally through studies correlating preoperative cognitive evaluations with postoperative assessments, and combining such data with imaging scans and surgical variables. These children should then be assessed at regular intervals over the course of their development. Inconclusive findings in the literature that has attempted to address this issue may in part be attributable to the difficulty in quantifying infant development with the available standardised assessment tools. Furthermore, as stated above, developmentally, one

might expect that any deficits incurred early in life may be evident at a functional level later on, as children mature.

7.7 Psychological Functioning

The findings with respect to the psychological functioning of the children in the present study revealed firstly, that as a group, children with syndromic and nonsyndromic craniosynostosis are not at increased risk of clinically significant psychological maladjustment, based on parent and teacher-rated internalising and externalising problem behaviour frequencies. Hence, parents need not necessarily expect psychosocial problems in school-aged children, even if the craniofacial deformities are severe as is common in some of the syndromic craniosynostoses.

There were no significant gender differences in problem behaviour frequencies on the measures administered. The frequency of internalising and externalising problem behaviours was not significantly different between the more severe craniofacial deformities of syndromic craniosynostosis and that of the nonsyndromic craniosynostoses, suggesting perhaps that severity of craniofacial deformity is not predictive of the likelihood for negative psychological outcome in these disorders. However, consistent with previous research into children with craniofacial anomalies (e.g. Kapp-Simon & Dawson, 1998; Speltz et al., 1993), there does appear to be increased risk of sub-clinical levels of internalizing, but not externalizing problem behaviours in children with craniofacial anomalies. A possible explanation for such behaviours (e.g. social withdrawal, behavioural inhibition) are that they represents a self-protective pattern to minimise peer rejection (Rubin & Wilkinson, 1995).

7.8 Methodological Issues

Although the statistical power of study findings may be tempered by the small sample size, a natural artefact of empirical investigations in the craniosynostoses, particularly the syndromic conditions, is the rarity of these conditions which makes it virtually impossible to find a sufficiently large sample of patients that would be optimal to study. Indeed, this has presented an ongoing challenge for researchers in the field. To maximize the reliability and generalisability of the present study findings, patients were recruited from the only tertiary referral centre for

craniofacial management in the State of Victoria. The researcher contacted by mail patients who met eligibility criteria for syndromic craniosynostosis and who were residing in Victoria during the recruitment phase. Follow-up contact was attempted with all non-respondents. A response rate of 41% was achieved. In the nonsyndromic craniosynostoses, patients were selected randomly from those meeting diagnostic and age criteria, and letters of invitation were forwarded until numbers matching the syndromic craniosynostosis sample were achieved. The final sample can be considered to be representative one of children with syndromic craniosynostosis, since this study essentially included all available children with syndromic craniosynostosis aged between 6-16 years who responded to an invitation to participate in the study. It is, however, acknowledged that those milder cases that may not present for medical attention may be missed. In addition, those responding to invitations in the nonsyndromic group may represent those with some concern about the general development of their child. Sample size limitations may be partially addressed in future studies by extending the timeframe of data collection (e.g. a decade). Combining data from multiple centres is another possibility.

It would be optimal to have compared this clinical sample with a normal control group, instead of using comparative normative test data, since the latter introduces the possibility of sampling bias, with resulting deviations from test standardization samples. However, this was conducted as an exploratory study to broadly describe the neuropsychological features of a sample of children who had previously not been studied at an empirical level in this age group, and on the range of measures administered. This represented an initial step in identifying future areas of research for this population that a worthy of further investigation. Given the time and resources allocated to a Doctoral research project, it was considered that examining a group of this nature, in detail, was a more efficient allocation of resources. This was furthermore justified by the availability of extensive psychometrically valid and reliable data that allowed comparison of this sample with that of normative population samples of Australian children, rather than an age-matched normal control group. The next step in this research domain will include comparison with a demographically matched control group.

A number of methodological limitations are relevant to this, and previous studies of the craniosynostoses.

The application of a cross-sectional study design to what is essentially a longitudinal issue presented some limitations to the theoretical questions that could be addressed in this study, particularly those relating to the timing of the emergence of cognitive difficulties in these conditions. The intention of this study was to conduct an exploratory investigation into these conditions. Future areas of research have been identified on the basis of this.

Another inherent problem of gathering clinical information on a retrospective basis is that data from a wide range of sources (e.g. genetics, neuroimaging) may not be routinely collected on all patients. Neuroimaging studies, for example, were only available for a selected number of participants, most of whom were at potential risk of cerebral pathology. A major barrier to progress in understanding the cognitive issues in the craniosynostoses has been the process of accruing well-defined psychometric data using rigorous techniques. The lack of specific data on neuropsychological outcomes in the craniosynostoses stems in part from the approach to the problem. There has been a justifiable dearth of psychometric literature addressing the timing of surgery as this relates to cognition. The longer-term developmental outcomes in these conditions have received considerably less attention. This study's key strength was the application of formal, standardised neuropsychological measures to evaluate specific cognitive domains, beyond that of general intellect in the craniosynostoses. Most studies that have attempted to quantify these cognitive skills are, however, limited by the non-standardised evaluation measures (e.g. hospital medical records, examiner-constructed questionnaires, school reports) utilised to achieve their aims. The present study furthered that of previous research by providing empirical support, using objective and standardised assessment tools, to demonstrate that children with craniosynostosis present with subtle cognitive deficits in specialised cognitive skills beyond that of general intelligence (Bottero et al., 1998; Kapp-Simon, 1998; Sidoti et al., 1996).

This research has also generated further areas of worthy investigation. The child and adolescent age group appears to be a period of development that is attracting increasing attention from researchers in the field. The findings of this study, and from a theoretical perspective, our knowledge of the implications for later development following early disruption to the central nervous system, highlight the significance of more studies in this area. These findings imply that psychometric

investigations should also incorporate more formal conceptualizations of neuropsychological differences in children with craniosynostoses than those that have guided previous research. Data from multicentre studies collected on a considerably larger cohort of children with different craniosynostosis conditions over an extended timeframe, and including a comparison group, is required to replicate and extend the findings from the present study. This would furthermore permit examination of the evolution of cognitive development in these conditions from birth to adulthood.

Long-term studies should be carried out for many specific syndromes with emphasis on the problems of adaptation and with specific suggestions about coping strategies for affected individuals and their families. Longitudinal studies are also needed to evaluate medical or surgical intervention in various disorders with emphasis on treatment timing and on changes in cognitive over the developmental lifespan.

A wide range of variables that may be important not only in predicting, but also in their effects on cognitive outcomes, such as cerebral pathology and chromosomal anomalies, are acknowledged for their potential influence on the present study findings. However, it was beyond the scope of the present study's aims to evaluate and control for the effects of these variables. Future studies would ideally address these issues by conducting predictive and correlative analyses on these, and other known risk factors to cognition, such as socioeconomic status, family history, brain malformations and pre- and postoperative risk factors. The collaborative efforts of key personnel involved in the management of craniofacial conditions are necessary to achieve these aims. Combining data from multiple sources, specifically neuropsychological, craniofacial surgery, speech pathology, neuroimaging and molecular studies would enable craniofacial subtypes to be delineated and distinguished on the basis of clinical and molecular features with greater precision, and also allow us to identify markers of severity. The variation in methodological approaches to the measurement of cognition in the craniosynostosis across studies however, hampers efforts to combine data from different sources, and hence such an approach requires careful planning to formulate comparable assessment protocols across sites. Such data would ultimately improve diagnosis and management, as well as stimulate further research, in these disorders.

An area deserving of further attention is that of the correlates of sutural location and cognitive dysfunction. There may be regional differences in the sites of synostosis with respect to cognitive outcomes (e.g. increased presence of memory deficits with temporal region involvement).

Research into craniofacial disorders should maximize opportunities provided by technological advancements in the neuroimaging field. Recent studies using semi-automated and automated analyses of MR scans have revealed brain abnormalities in children with speech and language impairment (Jernigan, Hesselink, Sowell, & Tallal, 1991) and inherited speech and language disorders (Watkins et al., 2002). This provides a promising field of further investigation alongside psychometric data in the craniosynostoses. These techniques, as well as functional analysis techniques of cortical activity (e.g. position emission tomography, functional MRI and event-related potential studies), may enable us to examine the cortical distribution of cognitive functions in the craniosynostoses. In addition, surgical factors, for example, could be investigated through combining data from pre- and post-operative neuroimaging studies (e.g. CT, MRI scans) and psychometric evaluations.

Most studies on the psychological characteristics of the craniofacial disorders have focused on the cleft lip and/ or palate population, with craniosynostosis conditions, when studied, typically included as a minor subset of larger samples of different craniofacial disorders. It is important that future prospective and clinically relevant research that focuses on craniosynostosis-only samples is conducted so that subtle differences between these and other craniofacial disorders can be elucidated. Longitudinal investigations that allow for more detailed examination of psychological processes (e.g. self-esteem, body image) than that possible in this study is required to better understand the clinical needs of this population. It is also important that data on psychological variables should be examined alongside cognitive data, so that the predictive and correlative factors of internalising problem behaviours can be explored, as these relate to cognitive processes. For example, the underlying etiology of social isolation may differ across individuals. For some, this may reflect a lack of social skills, negative self-concept or self-esteem. For others, cognitive limitations may limit the child's capacity to comprehend and reciprocate conversations due to information processing or language difficulties, or interpret social cues, in interactions their age-matched peers.

7.9 Summary and Conclusions

The findings from this study have made a significant contribution to the understanding of the development implications of craniosynostosis. It is one of the first to provide a detailed, quantitative characterisation of the long-term neuropsychological outcomes in children and adolescents with this condition, an age group which has been poorly addressed in the psychological literature on these conditions.

Broadly, this research has shown that the craniosynostoses have widely heterogeneous cognitive outcomes, and also, findings point to an increased risk of organic dysfunction in children with syndromic, as well as, nonsyndromic, craniosynostosis who have undergone an accepted corrective surgical procedure for the condition. The two main outcomes that emerged from this study were, firstly, wider variability in cognitive outcomes in the syndromic craniosynostoses than previously acknowledged, with many of the children in this study being of normal intelligence. Secondly, we identified the presence of mild to moderate neuropsychological deficit in children with nonsyndromic craniosynostosis, a disorder considered to be relatively benign with respect to cognitive outcomes.

The syndromic craniosynostoses, which have been traditionally regarded as being synonymous with intellectual dysfunction in the literature, displayed intellectual capabilities that suggest that low intelligence is not an inevitable feature of these conditions. Furthermore, many of these children attended mainstream schools and were matching their peers academically. These findings certainly present a more optimistic outlook for patients and families affected by craniofacial disorders and highlight the importance of not unduly lowering expectations for these individuals on the basis of their conditions. This can serve to only compound existing problems, and, furthermore, exaggerate differences from their non-afflicted peers.

This study has provided important information about the developmental implications for children diagnosed with craniosynostosis. The identification of mild to moderate neuropsychological dysfunction in school-aged children with nonsyndromic craniosynostosis is a particularly significant finding. These deficits, specifically affecting attention and executive cognitive skills, could not be explained by intellectual status, since this group was of average ability. Findings contradict much of the early literature that regarded nonsyndromic craniosynostosis

as being without functional cognitive consequence, and furthermore challenges the notion that cosmetic factors are the only important considerations in these conditions. The risk of cognitive dysfunction should be addressed as a pertinent consideration in the treatment protocols of affected patients.

A significant limitation of previous studies in the child and adolescent age group is the limiting focus taken by quantifying intellectual features of these children, in isolation. Of those studies purporting to be neuropsychological in nature, a comprehensive description of the array of cognitive skills that are typically measured as part of a neuropsychological assessment, have not been studied in the same sample. A neuropsychological evaluation can detect areas of specific strength and deficit, which are not necessarily detectable on global intelligence assessment alone. The importance of a comprehensive assessment was illustrated by the findings of this study; despite being of seemingly 'average' general intelligence, children with nonsyndromic craniosynostosis displayed a combination of cognitive deficits that had potentially significant implications for everyday functioning.

These findings lend support for contemporary developmental neuropsychological theory that proposes that prenatal brain injury can have significant implications for long-term development, and, furthermore, implicates anterior cerebral regions as most vulnerable to the effects of such disruptions to normal CNS maturational processes.

This study was conducted as an exploratory investigation. A principle objective of this research was to identify avenues that warranted further investigation in the craniosynostoses. This study raised many unanswered questions. On the basis of these research findings and, clinical experience, the most effective approach to studying these conditions would appear to be multidisciplinary in nature, Any attempt to make predictions and prognoses about the craniosynostosis needs to take into consideration the wide, and complex, range of factors that contribute to cognitive outcomes. Hence, future studies that address the cognitive features of the craniosynostoses would ideally involve geneticists, plastic surgeons, neurologists and speech pathologists, and endeavour to establish the interrelationships between data from these multiple sources.

7.10 Management and Intervention Recommendations for the Craniosynostoses

These study findings have raised important considerations for the patient management protocols of craniofacial disorders, and can inform management and intervention practices for the treatment of these conditions.

Often parents will be warned about the possible need for surgery and prognosis. Study findings suggest that, particularly in the nonsyndromic single-sutural conditions for which surgery is typically advocated on cosmetic grounds, the implications upon cognition may be more significant than previously thought. Parental counseling and treatment planning for children with craniosynostosis should address the possibility of cognitive impairment in affected individuals.

Our results reinforce the principle that all children born with craniofacial conditions require careful and detailed psychometric assessments from an early age. As other authors contend, (e.g. Speltz et al., 1997), these children should be monitored over time, at key stages in their development, and extending into the school age years. In addition to evaluation of intellect, a comprehensive appraisal of a wide range of cognitive skills, such as attention, memory and new learning and executive cognitive functions should be routinely performed at an age when these abilities can be reliably measured, since, as this study has highlighted, intellectual evaluation alone may overlook dysfunction in these more specific cognitive domains. The at times, subtle nature of cognitive deficits in the craniosynostoses, mandates closer and more detailed inspection of the cognitive profiles of these patients on an individual basis.

This study showed that children with craniosynostosis can have cognitive impairments in areas that play an important and significant role in an array of everyday living skills and behaviour, including educational demands. Such impairments may have wide-reaching implications for children who may be unable to keep up with their peers in a variety of circumstances. Lezak states that executive functions are "capacities that enable a person to engage successfully in independent, purposeful, self-serving behaviours" (Lezak, 1995, p42.). Lezak further argues that the integrity of these functions is necessary for appropriate, socially responsible conduct. The adolescent years are a time in which demands for independent thinking and self-management are particularly pertinent. Executive

cognitive deficits can, to some degree, be amenable to remediation strategies; indeed, relatively simple procedural interventions can often make larger differences in performance. Detailed characterisation of specific cognitive strengths and weaknesses also enables treatment interventions and management protocols to be formulated with greater precision, and ensures that optimal educational placements, learning support and therapeutic interventions to be implemented (e.g. modifications to home and classroom based instruction and routines).

Craniofacial anomalies in a child or adolescent represent both an adaptational and psychological challenge for the affected patient and family, and a treatment challenge for the interdisciplinary craniofacial team. Information obtained from cognitive assessment can be effectively used to determine and shape the psychological support for children where required, based on their profile of cognitive strengths and weaknesses. For example, behavioural management strategies using positive reinforcement (e.g. rewards system) may be more successful in modifying problematic behaviour in a child with an intellectual disability than attempting reasoning and problem-solving solutions to modify such behaviour. Similarly, encouraging participation in enjoyed activities may be effective in promoting self-confidence and self-esteem rather than psychological counseling in which such issues are explored in detail.

In conclusion, within the constraints of the study's goals, this exploratory study nevertheless represents some important advances on previous research in the psychometric literature on the craniosynostoses, and has made an initial step in addressing important areas of further investigation. Our findings highlight the need for additional clinical, epidemiologic and cognitive research into populations of craniosynostosis to more clearly elucidate the characteristic needs, and assist with refining psychological treatment and remediation protocols for individuals with craniosynostosis throughout their lifespan.

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Appendix A Syndromes associated with craniosynostosis and their clinical features

Syndrome	Clinical Features
Crouzon syndrome	Craniosynostosis Shallow orbits with proptosis Strabismus Midface hypoplasia
Apert syndrome	Craniosynostosis Proptosis Hypertelorism Syndactyly of fingers and toes
Pfeiffer syndrome	Craniosynostosis Proptosis Strabismus Ocular Hypertelorism Down-slanting palpebral fissures Broad thumbs and great toes Midface hypoplasia Variable syndactyly of fingers and toes
Saethre-Chotzen syndrome	Craniosynostosis Facial asymmetry Low-set frontal hairline Ptosis of the eyelids Deviated nasal septum Variable syndactyly

Appendix B Diagnostic Classification of Craniosynostosis

International Classification of Diseases (ICD-9-CM and ICD-10-AM) diagnostic codes for selection of patients with craniosynostosis-related disorders

ICD-9-CM

754 Certain congenital musculoskeletal deformities

754.0 Of skull, face and jaw

- *Asymmetry of face*
- *Doliocephaly*
- *Plagiocephaly*

755.5 Other anomalies of upper limb, including shoulder girdle

755.55 Acrocephalosyndactyly

Apert's syndrome

756.0 Anomalies of skull and face bones

756.0 Craniosynostosis

- *Acrocephaly*
- *Imperfect fusion of the skull*
- *Oxycephaly*
- *Premature closure of the cranial sutures*
- *Tower skull*
- *Trigonocephaly*

756.01 Craniofacial dysostosis

Crouzon's disease

ICD-10-AM

Q67 Congenital musculoskeletal malformations deformities of head, face, spine and chest

Q67.3 Plagiocephaly

Q75 Other congenital malformations of skull and facial bones

Q75.0 Craniosynostosis

- *Acrocephaly*
- *Imperfect fusion of the skull*
- *Oxycephaly*
- *Trigonocephaly*

Q75.1 Craniofacial Dysostosis

- Crouzon's disease

Q87 Other specified congenital malformation syndromes affecting multiple systems

Q87.0 Congenital malformation syndromes predominantly affecting facial appearance

- *(including) Acrocephalyosyndactyly [Apert]*

Appendix C Parent Neuropsychological Questionnaire

PARENT QUESTIONNAIRE NEUROPSYCHOLOGICAL HISTORY

This questionnaire was developed to obtain basic information about your child so that we can make the best use of our time together. You are not likely to remember every detail of your child's development, so it is not necessary to spend a lengthy period of time struggling with a particular point. Whatever information you may be able to provide will be helpful. If there are any specific questions that seem unclear, please mark them so that they can be clarified later.

1. CHILD'S PERSONAL HISTORY

Child's Name:_____Sex:___
Date of Birth:_____Age:___
Country of Birth:_____Language/s spoken at home:_____
_____
Grade: _____School: _____Teacher:_____
Left-handed/ Right-handed:____

2. FAMILY COMPOSITION

Please list all other children and immediate family members of your child. Indicate their names, sex, age and their relationship to your child (e.g. father, brother, step-sister)

Name	Age	Sex	Relationship to your child	Education/ Occupation

Do any other family members have craniosynostosis?

Name	Age	Sex	Relationship to your child	Education/ Occupation

Have any of your family members or relations had learning difficulties, behaviour problems or neurological disorders? If so, please describe the nature of their problems and their relationship to your child, e.g. aunt, cousin, etc.

_____
_____
_____
_____
_____

3. MEDICAL HISTORY

a) Pregnancy with this child

Were there any complications with your pregnancy with this child (e.g. anaemia, high blood pressure, diabetes, infections, hospitalisations, etc?)

_____
_____
_____
_____

Were there any medications/ drugs used during this pregnancy?
If yes, describe: _____
_____
Length of pregnancy:_____
Any complications:_____

b) Birth History

Length of labour
Complications during birth:

Induced _____
Caesarian _____
Forceps _____
Foetal distress _____
Breech (feet first) _____
Other (e.g. breathing problems, cord around neck)_____
_____
_____

c) Newborn

Birthweight _____
Blue at birth _____
Required oxygen _____
Had jaundice _____
Seizures _____
Other _____

4. DEVELOPMENTAL MILESTONES

Please indicate your child's age when he/ she achieved the following developmental milestones:

Milestone	Child's age
Sat alone	_____
Crawled	_____
Walked alone	_____
Spoke first words	_____
Spoke 2-3 words together	_____

Behaviour as a baby (e.g. eating, sleeping patterns, temperament)
_____
_____

Behaviour as a toddler (e.g. temperament, social skills)
_____
_____

5. CURRENT FUNCTIONING

Does your child miss school frequently because of illness? How frequently in the past year?
_____
_____

Please list any special tests your child has completed

Test	**Age**	**Where done**	**When**	**Results**
Hearing	_____	_____	_____	_____
Vision	_____	_____	_____	_____
EEG	_____	_____	_____	_____
Psychological	_____	_____	_____	_____
Neuropsychological	_____	_____	_____	_____
Speech Pathology	_____	_____	_____	_____

Other.....				

Does your child wear: Y/N
Prescription glasses _____
Hearing aids _____

6. CHILD PROFILE

Please tick the box that best describes the problems that your child is currently experiencing. Please comment further as you feel necessary.

	Major	Minor	None	Comments
Intellectual concerns				
General intellectual level				
Planning/ organisational skills				
Learning and remembering				
Comprehension				
Expression				
Other.....				
School Progress				
Reading/ word study				
Spelling				
Maths				
Sport/ Physical activity				
Willingness to go to school				
Relationship with peers at school				
Other.....				
Behaviour				
Disobedience				
Destructive/ aggressive				
Attention-seeking				
Daydreaming				
Impulsive				
Eating problems				
Other.....				
Social/ Emotional				
Self-confidence				
Relationship with siblings				
Relationship with parents				
Play with other children				
Other.....				
Current difficulties				
Medical				
Wetting				
Soiling				
Clumsiness				
Ability to use hands				
Skills in dressing/ eating				
Other.....				

7. ADDITIONAL COMMENTS

Describe what you see as your child's personal strengths

_____

_____

_____

Please provide any information that you think is relevant to this assessment

_____

_____

_____

Your name:_____ Relationship to your child:_____

Today's date: _____

Thank you for your cooperation in completing this questionnaire

Appendix D Parent/ Guardian Information Statement

Royal Children's Hospital, Melbourne

PARENT / GUARDIAN INFORMATION STATEMENT

Project No	21053A

Title of Project
Neuropsychological Functioning in Children and Adolescents with Craniosynostosis

Thank you for taking the time to read this Information Statement.
This information statement is 3 pages long. Please make sure you have all the pages.

Your child is invited to participate in a Research Project that is explained below.

What is the Research Project about?
Babies have skulls that have bone plates with gaps between them. These bone plates join together as they get older. In some individuals these join together too early. This is called craniosynostosis, and it has been shown to affect the thinking, learning and behaviour of some individuals with the condition. There is very limited information about the effects of craniosynostosis on the wide range of abilities, such as thinking, paying attention, remembering and behaviour that affect the day-to-day functioning of children and adolescents with the condition. In this study, we want to find out more about the thinking, learning and behavioural functioning of children and adolescents with different types of craniosynostosis.

Who are the Researchers?
There are seven researchers involved in this study: Annette Da Costa, Dr Alan Tucker, Ms Izabela Walters, Ms Jacquie Wrennall, Dr Anthony Holmes, Dr John Meara, and Dr Ravi Savarirayan. Annette Da Costa is a student at Victoria University currently completing a Doctorate in Clinical Neuropsychology. Dr Alan Tucker and Ms Izabela Walters are Clinical Neuropsychologists and staff members at Victoria University. Ms Jacquie Wrennall is the Neuropsychology Coordinator at the Royal Children's Hospital (RCH). Dr Anthony Holmes is the Director of the Department of Plastics and Maxillofacial Surgery at the RCH. Dr John Meara is an Honorary Surgeon with the RCH, specialising in Craniofacial Diseases. Dr Ravi Savarirayan is a Clinical Geneticist at the RCH.

Why am I and my child being asked to be in this research project?
Your child has been asked to participate in this project as she/he has been diagnosed with craniosynostosis and has attended the RCH for management of their condition.

What does my child need to do to be in this research project
By participating in this study, your child will be asked to complete a range of activities, including answering questions, pencil-and-paper and puzzle-like tasks. The assessment session will be conducted on one day, and will last approximately three hours, plus rest breaks every 30 minutes or earlier as needed. As the parent/ guardian, you will be asked to complete a series of questionnaires about your child's background development and current intellectual and behavioural functioning whilst your child is being assessed. Your child's teacher will also be asked to complete a questionnaire about your child's behavioural functioning at school.

Is there likely to be a benefit to my child?

There may be no benefit to your child from his/ her participation in the study. However, you and your child will have the opportunity to have a feedback session about the individual assessment results for your child. This information may assist you by gaining a better understanding of the thinking, learning and behavioural abilities of your child.

Is there likely to be a benefit to other children in the future?

Yes, there is likely to be a benefit to other children in the future. Gaining a better understanding of the thinking, learning and behavioural abilities of children and adolescents with craniosynostosis may help guide others to provide better information and support to other children and their families about the functioning of individuals with craniosynostosis. This information may also assist in the future design of better interventions for children and adolescents with craniosynostosis.

What are the possible risks and/or side effects for my child?

There are no anticipated risks and/ or side effects associated with your child's participation in this study.

What are the possible discomforts and/or inconveniences for me or my child?

Most children enjoy these activities. To allow for fatigue, the assessment sessions will include rest periods for half an hour every hour, or earlier if needed. Should your child become upset or distressed during the assessment, testing will cease immediately, and you and your child can discuss whether you would like to continue. You and your child may be inconvenienced by having to attend the RCH for the assessment, however we will try to minimise this as much as possible. If this is very inconvenient, it may be possible for your child to be assessed in your own home.

What will be done to make sure the information is confidential?

The information provided by you and your child will be treated as confidential. Your child's name and assessement material will be identified by a code number only, and will only be known to those involved in the research project. Any published results will not contain individual identifying information. Records will be securely stored at the RCH under the supervision of Ms Wrennall.

Will I be informed of the results when the research project is finished?

You and your child (where appropriate) will be provided the opportunity to have a feedback session to discuss the results of your child's assessment with the Principal Researcher and a report will be provided if requested. At the completion of the study, a summary of the overall research findings will be made sent to you. If there are any concerns about your child's functioning, a referral will be made for your child to the appropriate services and a neuropsychological assessment report will be provided, with your consent.

You can decide whether or not you would like to withdraw your child from this research project at any time. No explanation is needed.

You may like to discuss your participation in this research project with your family and with your doctor. You can ask for further information before deciding if your child will take part.

The name and telephone number of the person to contact for more information or in an emergency is:

Ms Jacquie Wrennall. Ph: (03) 9345-5512.

A Member of Women's & Children's Health

Flemington Road Parkville Victoria 3052 Australia

Telephone 03) 9345 5522 Facsimile 03) 9345 5789

http://www.rch.unimelb.edu.au

Date

For parents/guardians who speak languages other than English
If you would also like Information about the research and the Consent Form in your language, please ask for it to be provided.

What are my child's rights as a Participant?

1. I am informed that except where stated above, no information regarding my child's medical history will be released. This is subject to legal requirements.

2. I am informed that the results of any tests involving my child will not be published so as to reveal my child's identity. This is subject to legal requirements.

3. The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.

4. It has also been explained that my child's involvement in the research may not be of any benefit to him or her. I understand that the purpose of this research project is to improve the quality of medical care in the future.

5. I have been asked if I would like to have a family member or a friend with me while the project is explained to me.

6. I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).

7. I understand that this research project has been approved by the Royal Children's Hospital Ethics in Human Research Committee on behalf of Women's and Children's Health Board.

8. I have received a copy of this document.

If you have any questions about patient rights contact

The RCH Patient Representative
RCH Hospital Support Unit
Phone 9345 5676

Date

Royal Children's Hospital, Melbourne

PARTICIPANT INFORMATION STATEMENT

Project No	21053A

Title of Project
Neuropsychological Functioning in Children and Adolescents with Craniosynostosis

Thank you for taking the time to read this Information Statement.
This information statement is 2 pages long. Please make sure you have all the pages.

You are invited to participate in a Research Project that is explained below.

What is the Research Project about?
Babies have skulls that have bone plates with gaps between them. These bone plates join together as they get older. In some individuals the bone plates join together too quickly. This is called craniosynostosis. We do not know much about how craniosynostosis affects the day to day activities of children and adolescents. Some kids have difficulties with thinking, learning, and behaviour. Other kids do not have difficulties in these areas. In this study, we want to find out more about the wide range of abilities, such as thinking, learning, and behaviour, of children and adolescents with different types of craniosynostosis.

Who are the Researchers?
There are seven researchers involved in this study: Annette Da Costa, Dr Alan Tucker, Ms Izabela Walters, Ms Jacquie Wrennall, Dr Anthony Holmes, Dr John Meara, and Dr Ravi Savarirayan. Annette Da Costa is a student at Victoria University currently completing a Doctorate in Clinical Neuropsychology. Dr Alan Tucker and Ms Izabela Walters are Clinical Neuropsychologists and staff members at Victoria University. Ms Jacquie Wrennall is the Neuropsychology Coordinator at the Royal Children's Hospital (RCH). Dr Anthony Holmes is the Director of the Department of Plastics and Maxillofacial Surgery at the RCH. Dr John Meara is an Honorary Surgeon with the RCH, specialising in Craniofacial Diseases. Dr Ravi Savarirayan is a Clinical Geneticist at the RCH.

Why am I being asked to be in this research project?
You are being asked to be in this project because you have come to the Royal Children's Hospital for management of your craniosynostosis, and you are aged between 7 and 16 years of age.

What do I need to do to be in this research project?
You will be asked to complete a wide range of activities, such as answering questions, pencil-and-paper and puzzle-like tasks. You will be asked to come to the Royal Children's Hospital for one day to do this, and the activities will take about three hours of your time, and you will also have regular rest breaks. Your parent/ guardian will also be asked to complete some written lists of questions about your background history and your intellectual and behavioural functioning. Your teacher will also be asked to complete one set of questions about your intellectual and behavioural functioning at school.

Is there likely to be a benefit to me?
There may be no benefit to you from taking part in this study. However, this information may help you and your parents/ guardians gain a better understanding of your thinking, learning and behaviour.

A Member of Women's & Children's Health
Flemington Road Parkville Victoria 3052 Australia
Telephone 03) 9345 5522 Facsimile 03) 9345 5789
http://www.rch.unimelb.edu.au

Is there likely to a benefit to other people in the future?
Yes, by participating in this study, we will gain a better understanding of how craniosynostosis effects people's thinking, learning and behaviour so that we can provide better information to other children and adolescents and their families about craniosynostosis. This knowledge will help guide others in helping children and adolescents with craniosynostosis in the future with their learning and behavioural needs.

What are the possible risks and/or side effects?
There are no risks and/ or side effects associated with your participation in this study.

What are the possible discomforts and/or inconveniences?
The assessment will take about three hours, and you will also have regular rest breaks. Most children enjoy the activities you will be asked to complete. However, if you become upset or do not want to continue with the session, it will be stopped immediately. You and your parent can then discuss whether you would like to continue. You may be inconvenienced by having to attend the RCH for your assessment, however we will try to minimise this as far as possible. If this is very inconvenient, it may be possible to see you in your own home.

What will be done to make sure the information is confidential?
The information provided by you and your parent/ guardian will be treated as confidential. A code number will be used instead of your name on all assessment material. Only those people involved in the research project will know this information. Any published results will not contain your name or any other identifying information. Records will be securely stored at the RCH under the supervision of Ms Wrennall.

Will I be informed of the results when the research project is finished?
Your parent(s)/ guardian(s) and you will have the opportunity for a feedback session to talk about the results of your assessment with a member of the research team, and a report will be provided if requested. If there are any concerns about your assessment results, a referral will be made to the appropriate services, with your and/ or your parents consent. When the study is finished, a summary of the overall research findings will also be sent to you and your parent(s)/guardian(s).

You can decide whether or not to take part in this research project.

You can decide whether or not you would like to withdraw at any time without explanation.

You may like to discuss participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part.

The name and telephone number of the person to contact for more information or in an emergency:
Ms Jacquie Wrennall. Ph: (03) 9345-5512

For people who speak languages other than English
If you would also like information about the research and the Consent Form in your language, please ask for it to be provided.

Appendix F Parent/ Guardian Consent Form

Royal Children's Hospital, Melbourne

STANDARD INFORMED CONSENT FOR PARENT / GUARDIAN TO GIVE CONSENT FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH PROJECT

Project No 21053A

Title of Project
Neuropsychological Functioning in Children and Adolescents with Craniosynostosis

Principal Investigator(s) Ms Annette Da Costa, Dr Alan Tucker, Ms Izabela Walters, Ms Jacquie Wrennall

Brief outline of research project including benefits, possible risks, inconveniences and discomforts (12 lines maximum)
Craniosynostosis is when the bone plates of a baby's skull join together too early. It has been shown to affect the thinking, learning and behaviour of some individuals with the condition. In this study, we will be assessing the intellectual and behavioural functioning of children and adolescents with craniosynostosis. Your child has been asked to participate in this project as she/ he has attended the RCH for treatment of their craniosynostosis. By participating in this study, you and your child will be asked to attend the RCH for one day. Your child will be asked to complete a range of activities, including answering questions, pencil-and-paper and puzzle-like tasks. This will take approximately three hours and will include regular rest periods. Should your child become very tired, upset or distressed during the assessment, it will be ceased immediately and you and your child can discuss whether you would like it to continue. You will be asked to complete a series of questionnaires about your child's background development and current intellectual and behavioural functioning while your child is being assessed. Your child's teacher will also be asked to complete a questionnaire about your child's behavioural functioning at school. You may be inconvenienced by attending RCH for the assessment, however we will try to minimise this as much as possible. If this is very inconvenient, an assessment in your own home may be possible. You will be provided with the opportunity for a feedback session to discuss your child's results, and a report if requested. If there are any concerns about your child's functioning, a referral will be made for your child to the appropriate services, with your consent.

I (Parent/Guardian name) _____
Parent / Guardian of (child's name) _____
voluntarily consent to him / her taking part in the above titled Research Project, explained to me by
Mr / Ms / Dr / Professor _____

I have received a Parent/Guardian Information Statement to keep and I believe I understand the purpose, extent and possible effects of my child's involvement. I have been asked if I would like to have a family member or friend with me while the project was explained.

I understand that if I refuse to consent, or withdraw my child from the study at any time without explanation, this will not affect my child's access to the best available treatment and care from Women's and Children's Health. (The Royal Women's Hospital OR The Royal Children's Hospital).

I understand I will receive a copy of this consent form.

PARENT GUARDIAN SIGNATURE _____ Date _____

I have explained the study to the participant who has signed above, and believe that they understand the purpose, extent and possible effects of their involvement in this study.

RESEARCHER'S SIGNATURE _____ Date _____

A Member of Women's & Children's Health
Flemington Road Parkville Victoria 3052 Australia
Telephone 03) 9345 5522 Facsimile 03) 9345 5789
http://www.rch.unimelb.edu.au

Appendix G Participant Consent Form

Royal Children's Hospital, Melbourne

STANDARD INFORMED CONSENT FOR PARTICIPANT TO PARTICIPATE IN A RESEARCH PROJECT

Project No 21053A

Title of Project
Neuropsychological Functioning in Craniosynostosis

Principal Investigator(s) Ms Annette Da Costa, Dr Alan Tucker, Ms Izabela Walters, Ms Jacquie Wrennall

Brief outline of research project including benefits, possible risks, inconveniences and discomforts (12 lines maximum)
Craniosynostosis is when the bone plates of the skull join together too early. It may affect the thinking, learning and behaviour of some people with the condition. In this study, we will be assessing the thinking, learning and behaviour of children and adolescents with craniosynostosis. You have been asked to be in this project as you have come to RCH for management of your craniosynostosis. To be in this study, you will be asked to come to RCH and complete a range of activities, including answering questions, pencil-and-paper and puzzle-like tasks, which will take about three hours of your time on the one day. You will also be given regular rest breaks. Whilst most children enjoy these activities, if you become upset or do not want to continue, the testing will be stopped immediately. You and your parent/ guardian can then discuss whether to continue or not. Your parent/ guardian will be asked to complete a series of written lists of questions about your background development and current intellectual and behavioural functioning on the day of your assessment session. Your teacher will also be asked to complete a set of questions about your functioning at school. You may be inconvenienced by having to come to RCH for the assessment, however we will try to minimise this as much as possible. If this is very difficult, it may be possible to see you in your own home.

I, _____
voluntarily consent to taking part in this research project, which has been explained to me by

Mr / Ms / Dr / Professor _____

I have received a Participant Information Statement to keep and I believe I understand the purpose, extent and possible effects of my involvement. I have been asked if I would like to have a family member or friend with me while the project was explained.

I understand that if I refuse to consent, or I withdraw from the study at any time without explanation, this will not affect my access to the best available treatment and care from Women's and Children's Health (The Royal Women's Hospital OR The Royal Children's Hospital.)
I understand that I will receive a copy of this consent form.

SIGNATURE _____ Date _____

I have explained the study to the participant who has signed above, and believe that they understand the purpose, extent and possible effects of their involvement in this study.

RESEARCHER'S SIGNATURE _____ Date _____

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