CRANIOSYNOSTOSIS
RELATIONSHIPS WITH COGNITIVE, BEHAVIORAL AND EMOTIONAL FUNCTIONING

door

Joris Joannes Barthelomeus van der Vlugt

Craniosynostosis: relationships with cognitive, behavioral and emotional functioning
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CRANIOSYNOSTOSIS
RELATIONSHIPS WITH COGNITIVE,
BEHAVIORAL AND EMOTIONAL FUNCTIONING

Craniosynostosis
de samenhang met cognitief, gedragsmatig en emotioneel functioneren

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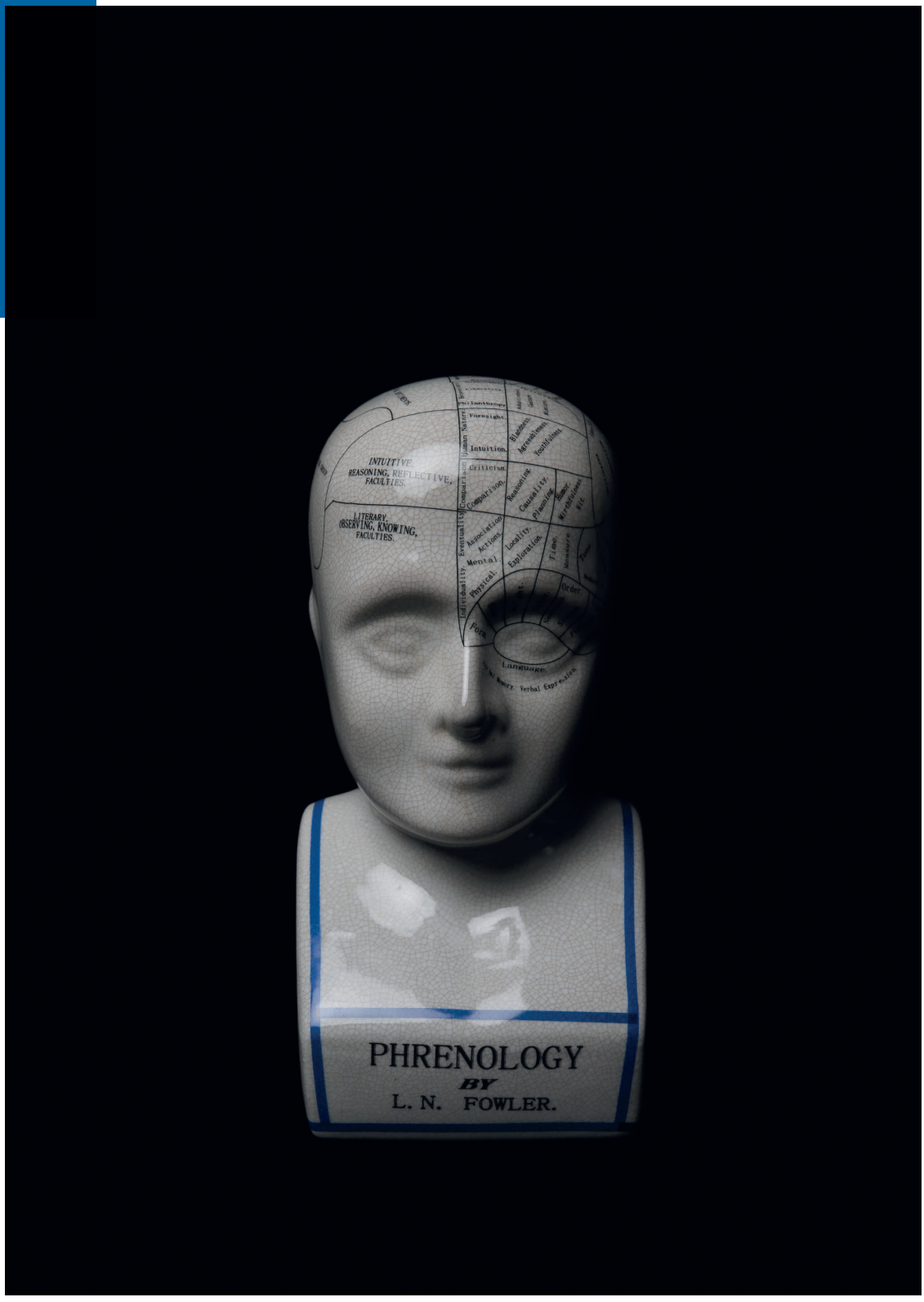
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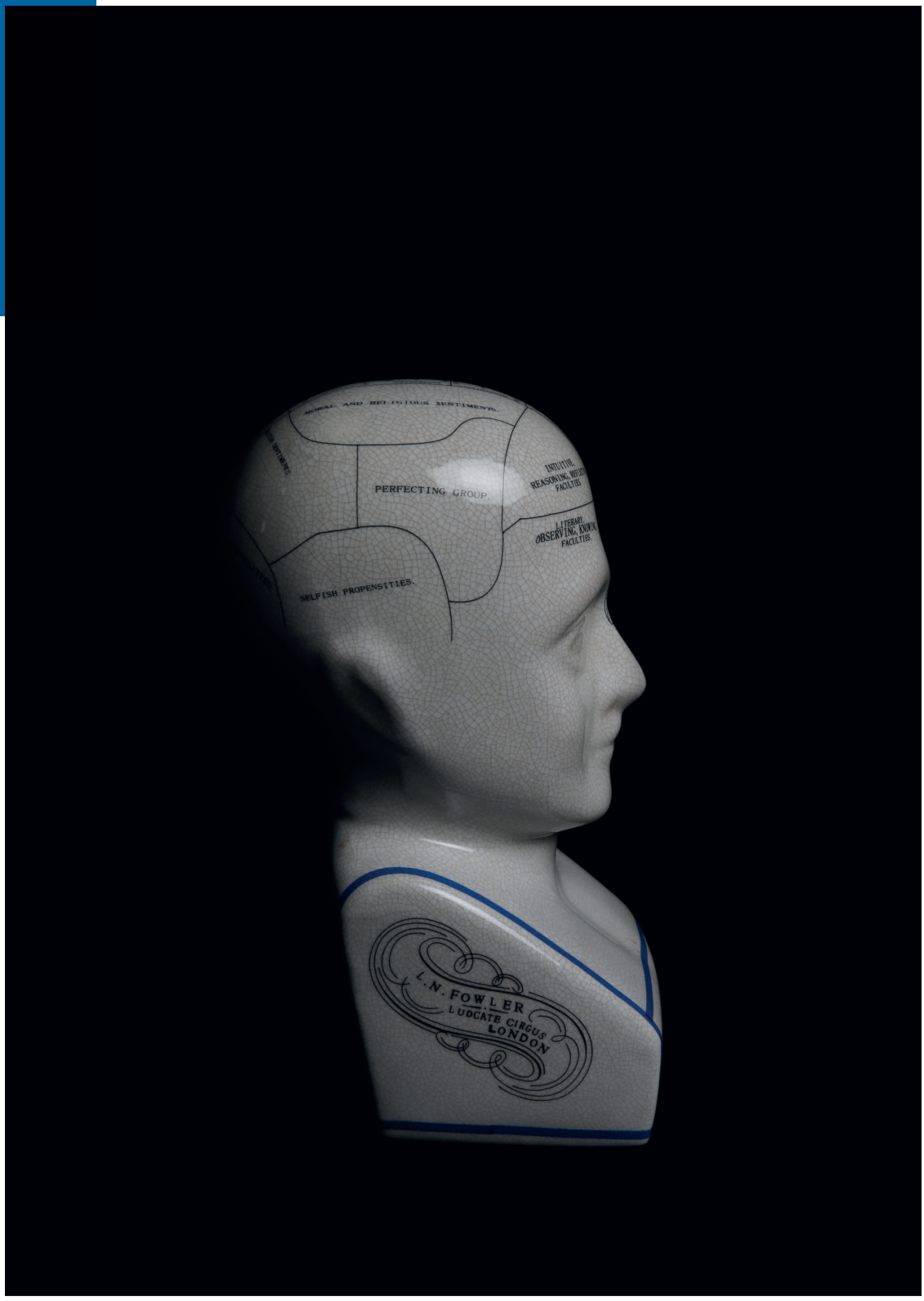
PART I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CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Background

In a normally developing infant skull, fibrous joints (sutures) separate the bony plates to permit temporary overlap as the human head becomes compressed while passing through the birth canal (Figure 1). Also, these sutures facilitate the enormous skull expansion necessary to accommodate brain growth during the peak period, which extends from mid-gestation until several years after birth (Dobbing & Sands, 1979). Cranial sutures close in a specific order. First, the posterior suture closes at 2 months after birth, followed by closure of the metopic suture in the first year of life, and the anterior fontanel after the second year of life (Tunnessen, 1990). The remaining sutures close in adulthood (Tunnessen, 1990). After the age of approximately 6 years, skull growth is taken over by bone resorption at the inner side of the skull and appositional bone growth (Cohen, 2000).

Figure 1. Sutures of the skull in normal development.

Craniosynostosis is a congenital condition that refers to the premature fusion of one or more of the fibrous sutures. This condition can result in restricted growth perpendicular to the affected suture and compensatory growth in unfused bony plates, producing an altered head shape. This results in a large variety of phenotypes, depending on the location and number of premature fusions (Virchow, 1851). For example, premature fusion of the metopic suture leads to a triangular, or wedge-shaped forehead (trigonocephaly) (Figure 2).

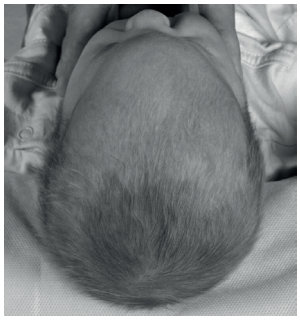

Figure 2. Photograph of a 9-month-old boy with trigonocephaly.

Craniosynostosis is the most common congenital skull deformity, with a prevalence ranging from 3.1 to 6.4 per 10,000 live births (Boulet, Rasmussen & Honein, 2008; Cohen, 2000; French, Jackson & Melton, 1990; Kweldam, van der Vlugt & van der Meulen, 2011; Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac & Renier, 1995). Subtypes of craniosynostosis are typically subdivided into two major groups:

1) Single-suture craniosynostosis (SSC), the most prevalent subtype (prevalence 2-3 in 10,000 live births (Kapp-Simon, Speltz, Cunningham, Patel & Tomita, 2007; Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac & Renier, 1996; Speltz, Kapp-Simon, Cunningham, Marsh & Dawson, 2004)) (Figure 3)
2) Complex forms of craniosynostosis (CC), which are either linked to a syndrome (40% of all types of craniosynostosis (Lajeunie et al., 2006)) or associated with more than one closed suture (about 5-15% of all types of craniosynostosis (Cohen, 2000)).

Most syndromes are associated with skull base abnormalities, midface hypoplasia and limb anomalies. The most common syndromes associated with complex forms of craniosynostosis are the Apert, Crouzon, Pfeiffer, Carpenter, Muencke and Saethre-Chotzen syndromes.

Scaphocephaly Trigonocephaly Brachycephaly Plagiocephaly

Figure 3. The most common phenotypes of single-suture craniosynostosis.

Craniosynostosis is associated with cognitive, behavioral and emotional problems (Knight, Anderson, Spencer-Smith & Da Costa, 2014). To date, however, the mechanisms behind these associations are still unclear. Therefore, the aim of this thesis is to gain more insight into the prevalence of cognitive, emotional and behavioral problems in craniosynostosis, and in potential mechanisms behind the related problems in children with craniosynostosis.

This chapter starts with a historical perspective on the relation between craniofacial malformations and cognitive, emotional and behavioral problems. Then, an overview is provided of research focusing on cognitive, emotional and behavioral problems in

craniosynostosis, as well as their interactions, in children with single-suture craniosynostosis and with complex forms of craniosynostosis. After outlining the existing theories that aimed to explain cognitive, behavioral and emotional problems in children with craniosynostosis, we describe the aims and research questions of the studies presented in this thesis.

Historical perspective on the relation between craniofacial malformations and behavioral and cognitive problems

Unfortunately, over the centuries, people who were born with an oddly-shaped skull were often rejected and considered to be 'cursed' and/or 'the work of the devil' (Strickler van der Meulen, Rahael & Mazolla, 1990). This attitude towards congenital craniofacial malformations still persists in many parts of the world, even though the intellectual development of individuals with craniosynostosis is often normal. Franz Joseph Gall (1758-1828), introduced the concept that different mental functions are located in different parts of the brain. After systematic observation and broad experimentation, Gall concluded that certain aspects of character (called *faculties*) were in direct relation with specific *organs* in the brain. This led to Gall's 'theory of phrenology', in which morphology of the skull was deemed to be related to the human character (Wikipedia, 2018). Gall's theory was extensively described in his classic work from 1976: *The Anatomy and Physiology of the Nervous System in General, and of the Brain in Particular* (Figure 4). This was later followed by other publications and journals (e.g. Figure 5) (Wikipedia, 2018). However, because the academic society at that time was unable to replicate his results, by 1860 phrenology was largely discredited. Nevertheless, the concept of cerebral localization related to phrenology remained an appealing idea for scientists. Eventually, this concept even contributed to considerable neurological discoveries and formed (in part) the basis of modern day neuroscience (Simpson, 2005).

Figure 4. The skull and its (proposed) corresponding areas of character.

Figure 5. Front page of the American Phrenology Journal, 1848.

Craniosynostosis has been described in the human species for at least 8000 years (Gerszten, Gerszten & Allison, 1998). Galen, and later Hippocrates, were the first to develop an early understanding of the role of cranial sutures and recognition of cranial vault deformities (Cunningham, Seto, Ratisoontorn, Heike & Hing, 2007). By the 16th century, several anatomists showed special interest in skull sutures and documented a broad range of different types of craniosynostosis (Della Croce, 1583; Hundt, 1501; Vesalius, 1543). To the best of our knowledge, Sömmering was the first to make a connection between the deviant skull shape and neurodevelopmental problems (von Sömmering, 1801). He hypothesized that stenosis of the skull in craniosynostosis caused growth restriction of the brain, resulting in neurodevelopmental problems. Furthermore, he made the first theoretical steps to develop a treatment for craniosynostosis (von Sömmering, 1801). His ideas led to the hypothesis that expanding cranial volume might prevent these problems. The first to report on surgical release of the cranial sutures in children with craniosynostosis was Dr. Lennelogue in 1890 (Lannelongue, 1890). He was the first to attempt to expand cranial volume in order to encourage brain development. Also, in 1892, Dr. Lane described a case of a 9-month-old boy with craniosynostosis who was suspected to be mentally disabled (Lane, 1892). The child's mother had asked Dr. Lane: "*Can you unlock my poor child's brain and let it grow*?" Despite extensively cautioning her about the risks and the experimental nature of the operation, the mother consented that her child should be operated. Although the procedure went well, unfortunately, the child died 14 hours after the surgery. Despite this, Dr. Lane subsequently performed the same procedure on another child with craniosynostosis who proceeded to show, according to the surgeon "*…unequivocal evidence of mental improvement*" after the operation. However, in 1894, after reviewing the first 33 cases of whom 15 had died, surgeons received opposition from Dr. A. Jacobi. He was the founder of pediatrics in the USA (Wikipedia, 2013) and severely criticized this type of neurosurgery. Dr. Jacobi addressed the International Pediatric Congress in Rome, and said: "*Is it sufficient glory to don a white apron and swing a carbonized knife, and is therein a sufficient indication to let daylight into a deformed cranium and on top of a hopelessly defective brain, and to proclaim a success because the victim consented not to die of the assault? No ocean of soap and water will cleanse those hands, no power of corrosive sublimate will disinfect the souls*." Jacobi's persuasive and chastening argument was so strong that craniectomy was practically abandoned for almost 30 years (Hemple, Harris, Svien & Holman, 1961).

In 1921, two years after Dr. Jacobi's death, the first reports dealing with the surgical treatment of craniosynostosis resurfaced, when Mehner published his technique of removing the fused cranial suture (Mehner, 1921). The surgical technique evolved in the following decades (Anderson & Johnson, 1956; Shillito & Matson, 1968) until the late 1960s, when

Paul Tessier made the surgical treatment of craniosynostosis and its sequelae more common practice (Tessier, 1967). Over the years, more theories behind the association between craniosynostosis and neurodevelopmental problems evolved. However, to date, overcoming growth restriction is still the basis for most of the modern surgical techniques in children with craniosynostosis.

Whether the surgical intervention lowers, enhances or (possibly) even hampers the risk of development of cognitive, emotional or behavioral problems remains a topic of debate. Meanwhile, to date, the vast majority of research on cognitive, behavioral and emotional outcomes in children with craniosynostosis included operated patients only. Nevertheless, Boltshauser et al. investigated difference in cognitive, behavioral and emotional outcomes in unoperated children with sagittal synostosis compared to their siblings (Boltshauser, Ludwig, Dietrich & Landolt, 2003); their study showed no significant difference in cognitive functioning or in psychological adjustment measured with the CBCL between patients and their siblings. Needless to say, a study including a control group of children *not* undergoing surgery is not feasible due to the major ethical issues involved. Consequently, more insight into the effects of surgery on the development of cognitive, emotional or behavioral problems in craniosynostosis can only be based on non-causal associations. Nevertheless, especially in the field of invasive surgery, non-causal associations are often the best type of evidence available.

Cognitive functioning in single-suture craniosynostosis

In craniosynostosis, assumptions about mental problems related to an abnormal skull shape often lead to considerable social discomfort among patients and their parents. However, these assumptions are often erroneous, because most children with craniosynostosis, especially those with SSC, have a normal (cognitive) development (Kapp-Simon et al., 2016; Speltz, Collett, Wallace & Kapp-Simon, 2016). Nevertheless, during the course of performing the studies in this thesis, two case-controlled studies reported that, at group level, children with SSC are at elevated risk for the development of cognitive problems (Kapp-Simon et al., 2016; Speltz et al., 2016). Overall, patients with SSC showed small but significantly lower intelligence levels than matched controls. Although most studies found no significant differences in cognitive functioning between the diagnostic subtypes (K. A. Kapp-Simon, 1998; Kapp-Simon, Leroux, Cunningham & Speltz, 2005; Speltz et al., 2007; Starr et al., 2007; Toth et al., 2007), a more recent study found that children with metopic, unicoronal, or lambdoid synostosis scored lower on nearly all measures of achievement and intelligence than did children with sagittal synostosis (Speltz et al., 2016). Moreover, in samples of patients with trigonocephaly alone, a relatively high prevalence of cognitive problems has

been found. For example, in a subsample of children with non-syndromal trigonocephaly extracted from Lajeunie et al's naturalistic cohort study, we estimated a prevalence of intellectual disability (ID) of 11% (17/159) (Lajeunie, Le Merrer, Arnaud, Marchac & Renier, 1998). The authors indicated that patients with trigonocephaly accompanied by extracranial anomalies (such as finger deviations and/or extra digits, ear anomalies, maxillofacial abnormalities and/or cardiac defects) without a known syndrome, seem to have the highest risk of cognitive or learning disorders when compared to trigonocephalic patients without extracranial anomalies (Lajeunie, Le Merrer, Arnaud, et al., 1998). Notably, the majority of patients with extracranial anomalies cannot be linked to any known syndrome (Lajeunie, Le Merrer, Marchac & Renier, 1998). Nevertheless, it seems highly plausible that, in the future, more syndromes will be determined in patients with SSC and with extracranial anomalies. Sidoti et al. (1996) reported a prevalence of ID of 12.5% (4/32). Bottero et al. (1998) also reported a higher prevalence of cognitive problems in their sample of 76 patients with trigonocephaly. However, both of these latter studies were based on data acquired from non-validated instruments, thus weakening their level of validity.

Cognitive functioning in complex forms of craniosynostosis

Probably due to its low prevalence, data on cognitive functioning in complex forms of craniosynostosis (CC) are scarce. Although the majority of patients with CC have normal intelligence profiles, some subgroups have a higher prevalence of ID compared to SSC or norm groups (Da Costa et al., 2006; Maliepaard, Mathijssen, Oosterlaan & Okkerse, 2014; Noetzel, Marsh, Palkes & Gado, 1985). Particularly patients with Apert syndrome are reported to more likely have ID (Maliepaard et al., 2014; Patton, Goodship, Hayward & Lansdown, 1988; Renier et al., 1996).

Behavioral and emotional problems in single-suture craniosynostosis

Only a few studies have investigated behavioral and emotional problems in patients with SSC. Some of these studies reported no differences in the rate of problem behavior in children with SSC compared to healthy children (K. A. D. Kapp-Simon, P., 1998; Virtanen, Korhonen, Fagerholm & Viljanto, 1999). However, Speltz et al. (1997) observed that 7-year-old children with sagittal synostosis showed higher levels of parent and teacher-reported behavioral and emotional problems than matched controls. Moreover, other studies on individual subgroups of SSC (like trigonocephaly) suggest a high prevalence of behavioral and emotional problems (Bottero et al., 1998; Shimoji, Shimabukuro, Sugama & Ochiai, 2002; Shimoji & Tomiyama, 2004; Sidoti et al., 1996). Sidoti et al. (1996) reported that 33% of their sample of trigonocephalic patients showed problem behavior, such as attention deficit/hyperactivity

disorder (ADHD) and aggressive behavior. Kelleher et al. (2006) described a 37% prevalence of ADHD and/or autism spectrum disorder in 63 patients with non-syndromic trigonocephaly (Kelleher et al., 2006). Bottero et al. (1998) observed behavioral and emotional problems in 31% of their sample. However, because most of these latter estimates were based on data obtained with non-validated instruments, with mostly small sample sizes, they should be interpreted with caution.

Behavioral and emotional problems in complex forms of craniosynostosis

Very few studies aimed to investigate behavioral and emotional problems and social adjustment in CC. Sarimski (2001) reported high levels of attentional/learning problems, and elevated scores on social problems and social withdrawal, measured with the Child Behaviour Checklist (Achenbach, 1991) in over half of a sample consisting of 20 patients with Apert syndrome (2001). Bannink et al. (2010) found that behavioral problems in children with CC were highly prevalent, especially in boys and in patients with Apert syndrome and Muenke syndrome. Maliepaard et al. (2014) observed that patients with CC obtained high scores on the CBCL/6-18 scales Total Problems, Internalizing, Social Problems, and Attention Problems, and were more likely to have a DISC-IV-P derived diagnosis of ADHD-any type, or ADHD-hyperactive impulsive type.

Interaction between cognitive functioning, and behavioral and emotional problems

Although data on behavioral and emotional problems in children with craniosynostosis are scarce, it appears that especially patients with trigonocephaly and CC are at risk of developing behavioral and emotional problems. However, most earlier studies, especially those focusing on trigonocephaly (Boltshauser, Ludwig, Dietrich, Landolt, 2003; Speltz, Collett, Wallace, Kapp-Simon, 2016; Sidoti, Marsh, Marty-Grames, Noetzel, 1996; Bottero, Lajeunie, Arnaud, Marchac, Renier, 1998), did not consider the intelligence level when interpreting the behavioral and emotional problems of these children. This is remarkable when considering that studies on children with ID *without* craniosynostosis show a strong negative association between intelligence levels and childhood behavioral and emotional problems (Baker, Blacher, Crnic & Edelbrock, 2002; Dekker, Koot, van der Ende, & Verhulst, 2002; Fergusson & Horwood, 1995; Hinshaw, 1992; King, State, Shah, Davanzo, & Dykens, 1997; Rapport, Scanlan & Denney, 1999; State, King & Dykens, 1997). Consequently, the increased prevalence of ID in patients with craniosynostosis (especially trigonocephaly) might suggest that it is not the craniosynostosis-related factors, but rather ID together with craniosynostosis, that is associated with behavioral and emotional problems in this patient group. Establishing whether or not ID might be an important moderating factor for

the development of behavioral and emotional problems in patients with craniosynostosis can be of clinical importance because cognitive problems, especially ID, are relatively easy to detect at an early stage of development. When signs of ID, as a possible early warning for behavioral and emotional problems, are noticed, practitioners could intensify their monitoring. If behavioral and/or emotional problems do evolve in those patients, deploying early intervention programs might result in better long-term outcomes (Dawson et al., 2010; Warren et al., 2011).

Pathophysiology behind cognitive dysfunction and behavioral and emotional problems

Until now, the mechanisms behind the development of cognitive dysfunction and behavioral and emotional problems in patients with craniosynostosis are largely unknown. Nevertheless, to the best of our knowledge, four different hypotheses have been described in the literature.

The ***first hypothesis*** proposes that increased intracranial pressure (ICP) is a predictor for neurodevelopmental problems in patients with craniosynostosis (Renier & Marchac, 1988). Especially CC is associated with higher levels of ICP (Greene, 1998; Tamburrini, Caldarelli, Massimi, Santini & Di Rocco, 2005; Thompson, Malcolm, Jones, Harkness & Hayward, 1995; Tuite, Chong, et al. 1996; Tuite, Evanson et al., 1996). In addition, CC is associated with more neurodevelopmental problems (Maliepaard et al., 2014; Patton et al., 1988; Renier et al. 1996). Nevertheless, neither of these findings provide evidence that high ICP is causally related to neurodevelopmental problems in all forms of craniosynostosis, or even in CC. One of the challenges in proving this hypothesis is that measurement of ICP requires a very invasive procedure. To measure ICP, a solid sensor, coupled to a pressure transducer, has to be placed 1-2 cm within the frontal brain parenchyma for at least several hours (Eide, 2006). Until now, literature on direct associations between increased ICP and neurodevelopment is very scarce. Indirect measurement of ICP seems to be a less invasive alternative. For example, the presence of generalized beaten-copper patterns (BCPs), also known as digital impressions or convolutional digitations (Figure 6), are associated with higher ICP (State, King & Dykens, 1997) and are frequently seen on skull radiographs of children with craniosynostosis (Bristol, Lekovic & Rekate, 2004; Guimaraes-Ferreira et al., 2001; Tamburrini et al., 2005; Tuite, Evanson, et al., 1996) but also in healthy children (Tuite, Evanson et al., 1996). According to observations in the classic study of Davidoff, BCP is a rare phenomenon in healthy children under the age of 18 months (Davidoff, 1936). Moreover, the severity of BCPs is greater in children with craniosynostosis compared with healthy controls (Tuite, Evanson et al., 1996). Until now, no study has investigated the association between BCP and neurodevelopmental problems.

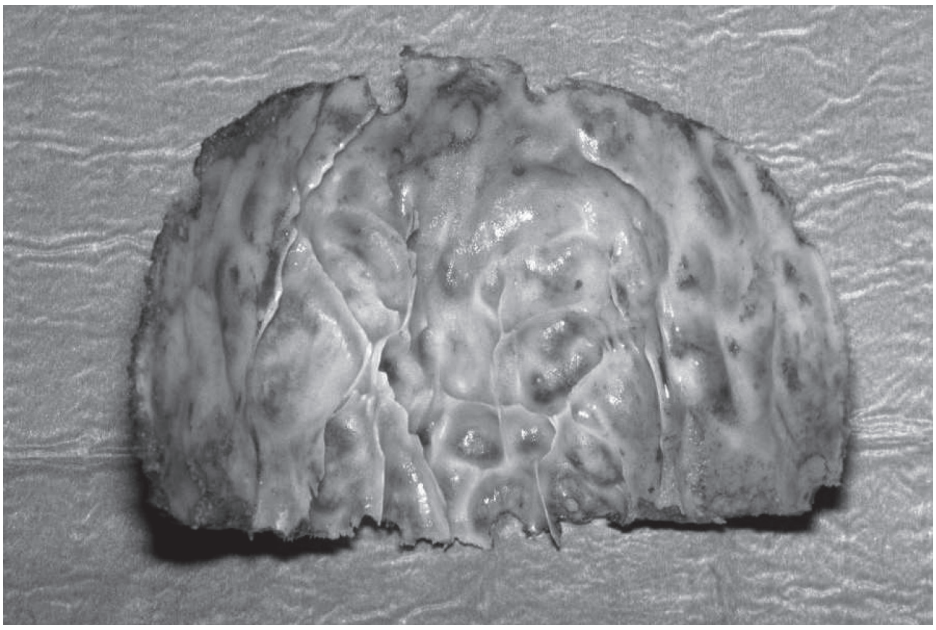

Figure 6. *Generalized beaten-copper patterns seen on a frontal bone that was extracted during cranial vault surgery.*

The domino effect of diminished skull growth leading to a smaller intracranial volume resulting in increased mechanical pressure between the skull and its content (brain, blood, and spinal fluid) is still considered to be the accumulation of events leading to cognitive impairment in patients with craniosynostosis. However, this 'mechanical' hypothesis is mainly based on older studies (Arnaud, Renier & Marchac, 1995; Renier & Marchac, 1988; Renier, Sainte-Rose, Marchac & Hirsch, 1982). For example, Sgouros observed that skull volumes of children with SSC (including trigonocephaly) aged 6 months or younger were smaller in comparison with healthy controls (Sgouros, 2005). To date, no study has investigated associations between hampered skull growth and neurodevelopment. Therefore, investigating associations between skull volume and cognitive functioning seemed an appropriate starting point to examine indications for the first hypothesis, as reported in this thesis.

The ***second hypothesis*** proposes that deformation of the brain, due to deformation of the skull, causes distress in cortical connectivity resulting in neurodevelopmental problems in craniosynostostis (Aldridge, Marsh, Govier & Richtsmeier, 2002; Carmel, Luken & Ascherl, 1981; Lin et al., 2006). Bottero et al. (1998) suggested that severe frontal stenosis was a strong predictor for cognitive and behavioral problems at a mean age of 6 years in a homogeneous sample of trigonocephalic patients. However, in their study, the use of non-

validated parental interviews may have biased their outcome and resulted in overrated negative parental judgment of (especially) patients with severe frontal stenosis. Three later studies (Mendonca et al., 2009; Starr et al., 2010; Warschausky et al., 2005) were unable to demonstrate an association between frontal stenosis and cognitive and behavioral function in patients with trigonocephaly. In these latter studies, however, cognitive functioning was assessed before the age of 3 years, which is reported to correlate poorly with later cognitive functioning (Roze et al., 2010). Thus, until now, the results related to the second hypothesis remain inconclusive.

The ***third hypothesis*** suggests that primary structural defects of the brain and skull originate from a common cause (Kjaer, 1995). Bottero et al. (1998) proposed a negative association between the presence of gross indicators of intracranial abnormality (e.g. frontal subdural space distention, hydrocephalus, and anomalies of the corpus callosum) on brain computerized tomography (CT), and long-term neurodevelopmental outcome. However, the use of non-validated parental interviews probably biased their outcome. Unfortunately, no other studies have examined possible primary malformations of the central nervous system underlying both craniosynostosis and associated neurodevelopmental problems. Interestingly, especially in children with trigonocephaly, a relatively high prevalence of corpus callosum anomalies and ventriculomegaly have been observed. Subsequently, it seemed logical to examine indications for a primary malformation underlying both craniosynostosis and cognitive and/or behavioral problems in these children.

The ***fourth hypothesis*** proposes that open craniofacial surgery itself, before age 2 years, could negatively influence long-term cognitive functioning. In the last decade, many studies have focused on the potential adverse effects of surgery at a young age on postoperative cognitive functioning. One hypothesis is that exposure to anesthetic agents during the peak period of brain growth (which extends from mid-gestation until several years after birth (Dobbing & Sands, 1979)) induces excessive neuronal apoptosis with a resulting decline in cognitive function (Jevtovic-Todorovic et al., 2003). An alternative non-mutually exclusive hypothesis, proposes that activation of inflammatory cytokines released by surgery-related tissue damage could result in postoperative cognitive impairment (McAfoose & Baune, 2009).

Since 2009, multiple clinical studies have examined whether cognitive development is deleteriously influenced by surgery in young children (Creeley, 2016). Two more recent studies, the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) (Sun et al., 2016) and the General Anesthesia compared to Spinal anesthesia (GAS) trial (Davidson et al., 2016), both suggest that the impact of short exposure to anesthetics (<85 min) early in life on cognition is limited (although the GAS study is still in progress).

Even though some earlier studies reported a significant negative association of (mostly) small surgical procedures on cognitive functioning in young children (Block et al., 2012; Flick et al., 2009; Ing et al., 2014; Naumann et al., 2012; Wilder et al., 2009), most failed to replicate this association (Bartels, Althoff & Boomsma, 2009; Davidson et al., 2016; Hansen et al., 2011; Kalkman et al., 2009; Sprung et al., 2009; Sun et al., 2016). However, this does not automatically exclude possible negative consequences for cognitive functioning after open craniofacial surgery.

To our knowledge, Nauman et al. (2012) is the only other group to include young children exposed to open craniofacial surgery. These authors found a non-significant trend for a negative association with total surgical time and a significant negative association between exposure to anesthetics and neurodevelopment. However, it seems reasonable to suggest that the lower number of patients in their subgroup exposed to open cranial vault surgery underpowered their outcome. Thus, more research is needed to further investigate possible negative effects of craniofacial surgery on neurodevelopment in childhood.

In this thesis, these four hypotheses are tested using available data (see Appendix). More knowledge on the pathophysiological mechanisms leading to cognitive dysfunction, and behavioral and emotional problems, might enhance early detection and prevention of developmental problems in children with craniosynostosis. Moreover, expanding knowledge on the pathophysiological processes towards cognitive and behavioral problems in children with craniosynostosis might improve our understanding of the broader concepts of neurodevelopmental problems in children.

Aims and research questions

The aim of the present thesis is to extend the existing knowledge on both the prevalence and etiology of (neuro)cognitive, behavioral and emotional problems in children with craniosynostosis.

In **Part 1** we report on the prevalence of (neuro)cognitive, behavioral and emotional problems in children with craniosynostosis, with additional focus on children with trigonocephaly, using validated instruments and taking intelligence level (IQ scores) into account.

Research questions:

- What is the prevalence of (neuro)cognitive, behavioral and emotional problems in different types of craniosynostosis?
- Are these problems more prevalent in children with craniosynostosis compared to the general population?

- Is intellectual disability a mediating factor in the association between emotional and behavioral problems in craniosynostosis, as it is in the general population?

In Part 2 we aim to extend the existing knowledge on the etiology of cognitive problems in children with craniosynostosis.

- Research questions to assess the association between intracranial pressure and cognitive functioning (***first hypothesis***):
- Is the quantity of preoperative beaten-copper skull patterns in patients with craniosynostosis under 18 months of age associated with postoperative cognitive functioning?
- Is preoperative skull size in patients with craniosynostosis associated with postoperative cognitive functioning?

Research question to assess the association between skull deformation and cognitive functioning *(**second hypothesis**):*

- Is the preoperative severity of the frontal stenosis in patients with trigonocephaly associated with postoperative cognitive functioning?

Research questions to assess the association between primary brain deformation and cognitive functioning *(**third hypothesis**)*

- Are primary brain anomalies associated with cognitive functioning in patients with trigoncephaly?
- Is the width of the central part of the lateral ventricles associated with cognitive functioning in patients with trigoncephaly?

Research questions to assess the association between open surgical treatment and cognitive problems *(**fourth hypothesis**)*

- Is duration of surgery of patients exposed to cranial vault surgery associated with postoperative cognitive functioning?
- Is cumulative exposure to anesthetics in patients exposed to cranial vault surgery associated with postoperative cognitive functioning?

Outline

To answer the research questions in **Part 1**, we retrospectively and prospectively assessed (neuro)cognitive, behavioral and emotional functioning in children with different types of craniosynostosis, with a specific focus on patients with trigonocephaly.

Data used in this thesis consisted of two samples. The first sample comprised a heterogeneous group of patients with craniosynostosis: described in **Chapters 2 and 4**. This sample consisted of the patient data of 138 patients (83 males, 55 females) from the National

Craniofacial Unit of the Erasmus Medical Center in Rotterdam. This sample was part of a larger cohort originally collected by Dr. J. M. E. Okkerse. The inclusion criteria were: diagnosed with craniosynostosis, aged between 5 and 16 years, and Dutch as the native language. All patients were born between 1978 and 1992.

The second sample consisted of a group of patients with only trigonocephaly: described in **Chapters 3, 5 and 6**. The sample comprised 82 patients with trigonocephaly, aged 4 to 18 years, from the National Craniofacial Unit of the Erasmus Medical Center in Rotterdam. Inclusion criteria for this study were: a diagnosis of metopic synostosis confirmed on a three-dimensional CT scan, and Dutch as the native language. Patients that met the inclusion criteria were born between 1990 and 2006.

In **Chapter 2** we retrospectively determined the prevalence of behavioral and emotional problems in different types of craniosynostosis, using validated instruments. Subsequently, we investigated the role of intelligence level (IQ scores) on behavioral and emotional problems in these different types of craniosynostosis. In **Chapter 3** we prospectively assessed behavioral and emotional problems among patients with trigonocephaly only, using validated instruments, and taking IQ scores into account. In addition, in this same group of patients, we also examined the percentage with intellectual disability, as well as associations between IQ scores and extra-cranial anomalies.

The aim of **Part 2** was to extend the current knowledge on the etiology underlying cognitive problems in patients with craniosynostosis. Accordingly, we investigated the four hypotheses (outlined above), all of which are suggested to play a role in the association between (neuro)cognitive, behavioral and emotional problems, and craniosynostosis. **Chapter 4** examined associations between preoperative beaten-copper skull patterns (before age 18 months) on skull radiographs of children with craniosynostosis and IQ scores, focusing on the hypothesis that a high ICP is the basis for cognitive problems in craniosynostosis (hypothesis 1). In **Chapter 5** we prospectively investigated associations between preoperative skull size and cognitive functioning in patients with trigonocephaly (also focusing on hypothesis 1). Subsequently, associations were studied between CT scan evaluation of the severity of preoperative frontal stenosis and IQ score, investigating the hypothesis that skull deformation is the basis for cognitive problems in craniosynostosis. Finally, we assessed whether primary brain anomalies in patients with trigonocephaly are associated with later cognitive functioning, focusing on the hypothesis that primary brain problems are the common cause of both cognitive problems and craniosynostosis. Furthermore, **Chapter 6** addressed the potential association between either duration of surgery or cumulative exposure to anesthetics in patients with trigonocephaly, by examining whether open cranial

vault surgery itself is related to cognitive dysfunction in patients with trigonocephaly (hypothesis 4).

Finally, in **Chapter 7** the main findings and conclusions drawn from Chapters 2 to 6 are presented and discussed, implications for clinical practice are addressed, and some recommendations are made for future research.

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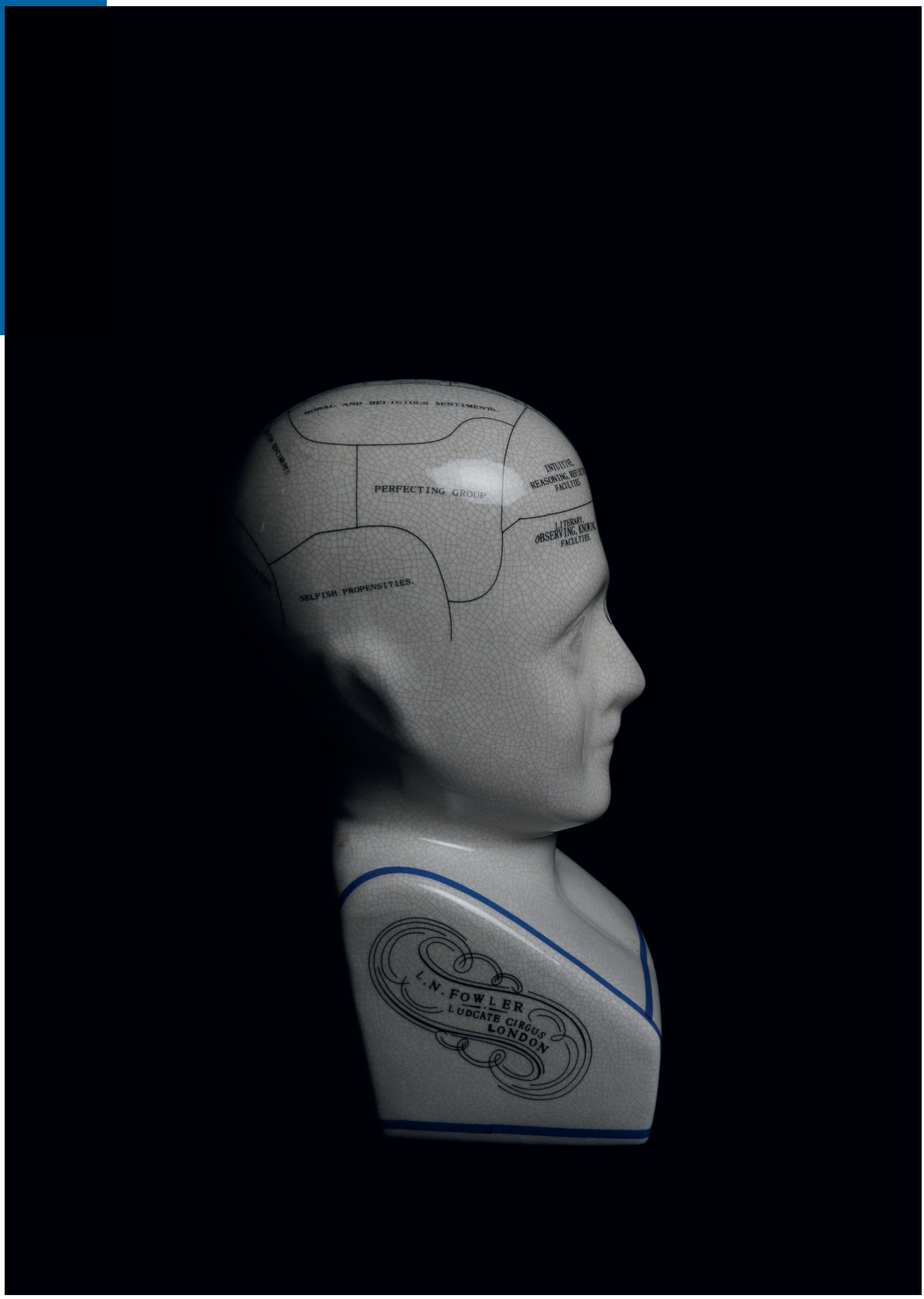
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CHAPTER 2

THE RISK OF PSYCHOPATHOLOGY IN CHILDREN WITH CRANIOSYNOSTOSIS

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ABSTRACT

Background: The purpose of this study was to assess the prevalence of behavioral and emotional problems in patients with craniosynostosis and to determine the prospective association of a beaten-copper pattern before 18 months of age with behavioral and emotional problems in patients with craniosynostosis.

Methods: The authors performed a follow-up study of 115 craniosynostosis patients at the Erasmus Children's University Hospital in Rotterdam. Behavioral and emotional problems were assessed with the Child Behavior Checklist at a mean age 8 years. The presence of beaten-copper pattern before the age of 18 months was assessed on presurgical radiographs. Analyses were adjusted for intelligence quotient.

Results: Whereas craniosynostosis patients with quotients of 85 or greater did not differ from children in the normgroup, craniosynostosis patients with quotients less than 85 had a higher risk of behavioral and emotional problems. However, these results were comparable to the findings of other studies assessing psychopathology in children with lower intelligence levels. Type of craniosynostosis (single suture versus complex) and a beaten-copper pattern before the age of 18 months did not affect the risk for behavioral and emotional problems in children with craniosynostosis.

Conclusion: When intelligence is taken into account, craniosynostosis is not associated with an increased risk of behavioral and emotional problems, nor is type of craniosynostosis or a beaten-copper pattern before the age of 18 months.

INTRODUCTION

Craniosynostosis is a relatively common skull malformation in which one or more skull sutures fuse prematurely. The incidence is approximately one in 2100 newborns (Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac & Renier, 1995). If untreated, craniosynostosis may lead to a lower intracranial volume which, even despite compensatory growth of the skull, is associated with increased intracranial pressure. Levels of 13 to 20 percent of increased intracranial pressure in single-suture synostosis (Eide, Helseth, Due-Tonnessen & Lundar, 2002; Gault, Renier, Marchac & Jones, 1992; Tamburrini, Caldarelli, Massimi, Santini & Di Rocco, 2005), and up to 40 percent in complex craniosynostosis (Pijpers et al., 2004; Renier, 1989; Renier, Sainte-Rose, Marchac & Hirsch, 1982; Tamburrini et al., 2005), have been reported.

Several authors have found a relation between increased intracranial pressure and problem behavior in craniosynostotic patients (Inagaki et al., 2007; Shimoji & Tomiyama, 2004; Siddiqi et al., 1995). They report, for example, a higher incidence of hyperactivity, irritability, inappropriate social interaction and even self-mutilation in children with increased intracranial pressure (Inagaki et al., 2007; Shimoji & Tomiyama, 2004; Siddiqi et al., 1995). In none of these studies, however, has a validated instrument been used to measure these problems, which makes it difficult to judge the reliability of their results. Furthermore, in none of these studies has the association between intelligence and problem behavior been considered. This is remarkable, because the risk of intellectual disability is relatively high in patients with craniosynostosis (Becker et al., 2005; Bottero, Lajeunie, Arnaud, Marchac & Renier, 1998; Da Costa et al., 2006; Lajeunie, Le Merrer, Arnaud, Marchac & Renier, 1998; Lajeunie, Le Merrer, Marchac & Renier, 1998). Several studies in children with intellectual disabilities (without craniosynostosis) have shown a negative correlation between intelligence and childhood problem behavior (Baker, Blacher, Crnic & Edelbrock, 2002; Dekker, Koot, van der Ende & Verhulst, 2002; Fergusson & Horwood, 1995; Hinshaw, 1992; King, State, Shah, Davanzo & Dykens, 1997; Rapport, Scanlan & Denney, 1999; State, King & Dykens, 1997). Dekker et al. (2002) found that the overall prevalence of behavioral and emotional problems in children with intellectual disability is nearly four times higher than in children from the general population.

The radiological sign of a beaten-copper pattern (Figure 1) is often considered as one of the indirect indicators of high intercranial pressure and is a common phenomenon in patients with craniosynostosis (Bristol, Lekovic & Rekate, 2004; Guimaraes-Ferreira et al., 2001; Tamburrini et al., 2005; Tuite et al., 1996). Remarkably, 71.6 percent of the craniosynostosis patients present with this pattern before the age of 18 months (van der Meulen, van der Vlugt, Okkerse & Hofman, 2008). In Davidoff's classic review of 2500 cranial radiographs,

beaten-copper pattern was shown to be common and related to age in healthy children. In contrast, beaten-copper pattern was uncommon in children younger than 18 months (Davidoff, 1936). It is assumed that the high prevalence of beaten-copper pattern in patients with craniosynostosis is attributable to the large increase in brain size in the first 2 years of life, in combination with restricted skull growth. This view is supported by the finding that in patients with complex forms of craniosynostosis higher percentages of beaten-copper pattern are seen (van der Meulen et al., 2008). A number of authors have addressed the link between beaten-copper pattern and increased intra- cranial pressure (Bristol et al., 2004; Eide et al., 2002; Greene, 1998; Guimaraes-Ferreira et al., 2001; Tuite et al., 1996). Tuite et al. (1996) noted a more severe and more generally located beaten-copper pattern in the craniosynostosis population and reported on a correlation between generalised beaten-copper patterns and significantly higher intracranial pressures. These results, combined with the finding that problem behavior and high intracranial pressure are more common in complex forms of craniosynostosis (Sarimski, 2001; Tamburrini et al., 2005; Thompson et al., 1995; Tuite et al., 1996), gave rise to the expectation of a relation between beaten-copper pattern and problem behavior.

The objective of this study was twofold. First, we aimed to assess the prevalence of behavioral and emotional problems in children with craniosynostosis, using validated instruments and controlling for intelligence. Second, we aimed to determine the prospective association between beaten-copper pattern before the age of 18 months and behavioral and emotional problems at a later age in patients with craniosynostosis.

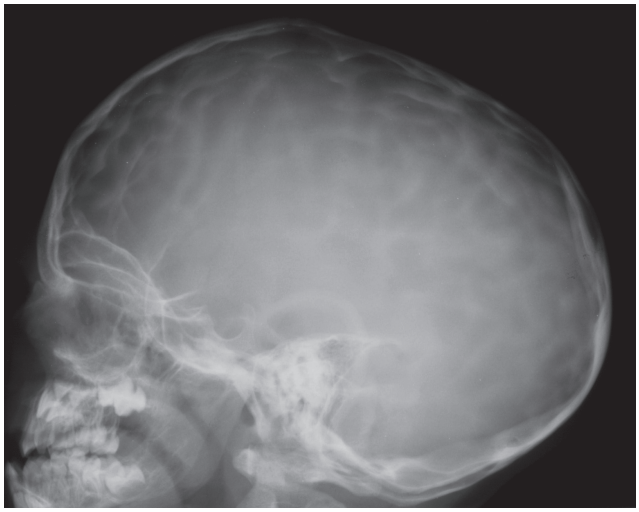

Figure 1. Generalised beaten copper pattern as seen on a lateral cephalogram

PATIENTS AND METHODS

Patient sample

All patients of the National Craniofacial Unit of the Erasmus Medical Center in Rotterdam that met the inclusion criteria (diagnosed with craniosynostosis, aged between 5 and 16 years, and Dutch as their native language) were asked to participate in the study. The final study sample consisted of 115 patients (response rate 73 percent, 73 boys, 42 girls) presenting with primary craniosynostosis. Reasons for not participating (27 percent) were practical problems (e.g., lack of time, no means of transportation and unwillingness to keep the child from school). Furthermore, some families could not be found because of change of address. All patients included in this study were treated surgically with mean age at time of surgery of 1.8 years (SD=2.4 years).

Patients were born between 1978 and 1992. The mean age at the time of the psychological assessment was 8.2 years (SD=2.6 years). The patient population consisted of two craniosynostosis subgroups: 62 patients with single-suture craniosynostosis (plagiocephaly, trigonocephalie and scaphocephalie) and 53 patients with complex-craniosynostosis (brachycephaly, oxycephaly, cloverleaf skull, Crouzon, Saetre Chotzen, Apert, Cohen, Pfeiffer, Carpenter, Say-Meyer and Antley-Bixter syndromes).

The participating patients did not differ significantly in diagnosis (single-suture craniosynostosis versus complex-craniosynostosis), gender, or age from the nonparticipating patients.

PROCEDURE AND INSTRUMENTS

Psychopathology

The Child Behavior Checklist (Achenbach, 1991) (CBCL/4-18) was used to obtain standardized descriptions of the children's behavioral and emotional problems for the preceding 6 months. Good reliability and validity have been demonstrated for the Dutch translation of the Child Behavior Checklist (Verhulst, Ende, & Koot, 1996). The Child Behavior Checklist is a parent report questionnaire consisting of 118 problem items that are scored on eight empirically based syndrome scales that were derived by factor analyses: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. In addition, the broad-band scale Internalizing is the sum of the scales Withdrawn, Somatic Complaints, and Anxious/Depressed and the Externalizing scale is the sum of the scales Aggressive and Delinquent Behavior. The Total Problems score

is obtained by summing up all 118 problem items. A higher score indicates a higher level of problem behavior.

The borderline cut-off scores (93rd percentile for the syndrome scales and 82nd percentile for the Internalizing, Externalizing and Total Problems scales) of a Dutch normgroup were used to divide the patient sample into a group of children with problem behavior and a group without problem behavior.

The norm group of the Child Behavior Checklist consists of 2068 Dutch children, aged 4 to 18 years, whose parents filled out the Child Behavior Checklist. All of these children attended regular schools and none of them had been referred for professional help for behavioral or emotional problems in the previous year (Verhulst et al., 1996).

Intelligence

Depending on the age of the participants, intelligence quotients were measured with the Snijders-Oomen Nonverbal Intelligence Test-Revised (Snijders, Tellegen & Laros, 1988) or the Wechsler Intelligence Scale for Children–Revised (Haasen et al., 1986). Both intelligence tests have a mean score of 100 and a standard deviation (SD) of 15. Research has shown that these instruments have satisfactory psychometric properties (Haasen et al., 1986; Snijders et al., 1988; Van Doorn, 1992).

Beaten Copper Pattern

Radiographic records were derived from the hospital archives. Pre-operative radiographic records, assessed before the age of 18 months, were available for 68 of the 115 patients (59 percent). For the remaining 47 patients, radiographic records were either missing or were assessed when the patient was older than 18 months. The data of these 47 patients were excluded from the analyses on beaten-copper pattern. To determine the randomness of these missing values, an analysis of missing values was conducted using chi-square and t-tests. There was no significant difference with regard to age ($p=0.25$), sex ($p=0.75$), subtype of craniosynostosis ($p=0.95$), or IQ ($p=0.99$) between the patients with and without radiographic records.

The pre-surgical radiographs were taken after the first clinical visit at a mean age of 6 months (n=68, range = 1 day to 1.5 years, SD= 0.4 years). Evaluation of the radiographic records was carried out by two independent investigators using Image J software (Rasband, 1997). Frontal views were analysed in order to determine whether the Beaten Copper Patterns were distributed evenly over both cranial halves; the percentages of beaten-copper patterns were divided by 2 if the beaten-copper pattern appeared on only one side of the skull. The beaten-copper pattern was quantified on the lateral radiographs using the method previously

described by van der Meulen et al. (2008). In this method, the percentage of beaten-copper pattern area is compared with the total area (in which the pattern can appear), resulting in a 0-100 percent score. Inter-observer reliability was assessed by computing the intra-class correlation coefficient between the measurements of the independent investigators. The intra-class correlation coefficient (ICC) was found to be sufficient at 0.8.

Beaten-copper pattern before the age of 18 months was present in 47 of the 68 patients (mean percentage = 20.5 percent). For the present analyses, we dichotomized this score into group 1 with a beaten-copper pattern before the age of 18 months (n=47, mean percentage = 20.5 percent), and group 2 without a beaten-copper pattern before the age of 18 months (n=21, mean percentage = 0 percent).

Statistical analysis

Analyses were conducted in three phases. First, to ascertain the association between intelligence levels and problem behavior, we performed a Spearman rank correlation between intelligence level and the dichotomized Total Problem Score. Subsequently, we stratified the total group by intelligence (IQ >85, IQ 70-85, IQ <70). For each of the subgroups we performed binomial tests to assess the differences in prevalences of problem behavior between the patient sample and the norm population.

Second, for each of the dichotomized Child Behavior Checklist scales, a binary logistic regression analysis was performed to assess the difference in the risk of a deviant score between the single-suture synostosis and complex craniosynostosis patients, adjusting for intelligence quotient.

Finally, a Mann-Whitney U test was performed to assess the relation between the presence of a beaten-copper pattern and problem behavior (Child Behavior Checklist Total Problem Score) in children with craniosynostosis.

RESULTS

Comparing the craniosynostosis group with the normgroup, controlling for intelligence quotient:
Correlation analysis showed a significant association between intelligence and Total Problem Score (Spearmans rho = -0.35, $p<0.001$). In intellectually disabled (IQ<70) craniosynostotic patients (n=14), the prevalence of problem behavior was significantly higher compared to the general population. They had significantly higher prevalences on the Child Behavior Checklist Total Problems scale (64% $p<0.01$), the Internalizing scale (42% $p<0.01$) and the scales Somatic Complaints (21% $p<0.05$), Anxious Depressed (50% $p<0.05$), Thought Problems (21% $p<0.01$), and Attention Problems (50% $p<0.01$).

The craniosynostotic patients with intelligence levels from 70 to 85 (n=22) also showed a significantly higher prevalence of problem behavior when compared to the Child Behavior Checklist norm population: CBCL Total Problems scale (41% p<0.01), Internalizing scale (36% p<0.05), Social Problems scale (27% p<0.05), and Somatic Complaints scale (23% p<0.05).

In craniosynostotic patients with intelligence levels higher than 85, the prevalence of problem behavior did not differ significantly from that in the norm population. Results are described in *Table 1*.

Table 1 Proportion and frequency of problem behavior in craniosynostosis stratified for intelligence compared with the general population

	General population	IQ > 85 n=79 (29 Complex, 40 Single)		IQ 70-85 n=22 (8 Complex, 14 Single)		IQ<70 n=14 (10 Complex, 4 Single)	
	%	n	%	n	%	n	%
Withdrawn	7	4	5	1	5	1	7
Somatic Complaints	7	5	6	6	27***	3	21**
Anxious Depressed	7	5	6	2	9	1	7
Social Problems	7	5	6	5	23 **	7	50***
Thought Problems	7	0	0	4	18 ⊀	3	21**
Attention Problems	7	8	10	4	18 ⊀	7	50***
Delinquent Behavior	7	6	8	1	5	0	0
Aggressive Behavior	7	4	5	3	14	1	7
Internalising	18	14	18	8	36**	6	43**
Externalising	18	13	16	4	18	3	21
Total Problems	18	17	22	9	41***	9	64***

⊀ p< 0.10
** p<0.05
*** p<0.01

Comparing the Single-Suture Craniosynostosis versus the Complex Craniosynostosis group, controlling for intelligence quotient

Results from the logistic regression models, adjusted for IQ, indicated a very small but significant difference between the single-suture craniosynostosis and the complex craniosynostosis group on the subscale Withdrawn. Patients with single-suture sraniosynostosis were 1.04 times more likely to have a deviant score on this subscale (p<0.05). No significant differences in problem behavior were found between the single-suture craniosynostosis and the complex craniosynostosis group on any of the other subscales (all p-values >0.18).

The relation between beaten-copper pattern and psychopathology

The presence of a beaten-copper pattern before the age of 18 months was not related to the level of problem behavior (Total Problem Score) at 8 years of age (SD= 2.6 years) in patients with craniosynostosis (n=68, Z -0.27, Mann-Whitney U 473.0, p=0.79).

DISCUSSION

Intelligence is associated with psychopathology/problem behavior

This study shows that intelligence is highly associated with behavioral and emotional problems in children with craniosynostosis, just as it is in children without craniosynostosis (Da Costa et al., 2006; Dykens & Kasari, 1997; Lajeunie, Le Merrer, Marchac et al., 1998; Sarimski, 2001). Until now, many authors have reported a higher prevalence of problem behavior in children with craniosynostosis compared to children without craniosynostosis (Becker et al., 2005; Boltshauser, Ludwig, Dietrich & Landolt, 2003; Bottero et al., 1998; Kelleher et al., 2006; Sarimski, 2001; Shimoji, Shimabukuro, Sugama & Ochiai, 2002; Shimoji & Tomiyama, 2004; Sidoti, Marsh, Marty-Grames & Noetzel, 1996). However, in none of these studies was intelligence taken into account as a confounder, although research has shown that children with craniosynostosis, especially complex craniosynostosis, are at risk for intellectual disability (Da Costa et al., 2006; Lajeunie, Le Merrer, Marchac et al., 1998; Sarimski, 2001). It seems justifiable to assume that many of these results were biased by lower intelligence levels in the craniosynostosis groups.

This study shows that children with craniosynostosis and intelligence quotient ≥ 85 do not show a higher prevalence of behavioral and emotional problems than children in the normgroup.

Children with craniosynostosis and intelligence quotient less than 85 show a much higher prevalence of problem behavior than the normgroup, ranging from 41 percent Total Problem scores in the deviant range in patients with intelligence quotients from 70-85, to 61 percent in patients with intelligence quotients below 70. However, higher prevalences of problem behavior are also found in intellectual disabled children without craniosynostosis. Therefore, it seems reasonable to assume that the high rate of problem behavior that is often reported in patients with craniosynostosis has more to do with their level of intelligence than with their craniosynostosis.

Type of craniosynostosis (Single-Suture Craniosynostosis versus Complex Craniosynostosis) as predictor of psychopathology/problem behavior?

Our results indicate that the prevalence of problem behavior is not higher in children with complex craniosynostosis than in children with single-suture craniosynostosis. In fact, children with complex craniosynostosis even had a slightly smaller risk of a deviant score on one of the eight subscales (Withdrawn) of the Child Behavior Checklist when compared to the single-suture craniosynostosis group. This latter finding, however, might be the result of our small sample size, and is expected to have no clinical implication.

Our findings are not consistent with findings from a previous study that indicated that complex craniosynostosis is associated with a higher risk of problem behavior (Sarimski, 2001). This inconsistency might be explained by the fact that we adjusted our analyses for intelligence quotient. Consistent with previous research, our findings indicate that complex craniosynostosis is associated with lower intelligence levels when compared to single-suture craniosynostosis (Da Costa et al., 2006; Lajeunie, Le Merrer, Marchac et al., 1998; Sarimski, 2001). Thus, intelligence levels seem more important than type of craniosynostosis in predicting the development of behavior problems.

Beaten Copper Pattern as predictor of psychopathology/problem behavior?

Even though the beaten-copper pattern was a common sign on radiographs before the age of 18 months in this patient group, no association was found between beaten-copper pattern and problem behavior at a later age. This is interesting because the presence of beaten-copper pattern has been associated with increased intracranial pressure (Tuite et al., 1996), and increased intracranial pressure has been associated with problem behavior (Inagaki et al., 2007; Shimoji & Tomiyama, 2004; Siddiqi et al., 1995). Thus, while our findings confirm a higher prevalence of beaten-copper pattern in young craniosynostosis patients, they do not confirm the association between beaten-copper pattern and behavior problems. One possible explanation could be the currently used threshold of increased intra-cranial pressure of 15 mmHg (Minns, 1984). This may not be the actual threshold for pathological processes in the brain that may result in problem behavior. In addition, the duration of increased intracranial pressure necessary to induce beaten-copper pattern is unknown. Therefore, we do not know the minimal length and level of intracranial pressure needed for brain damage to develop. More research is needed to reveal the impact of higher intracranial pressure in the craniosynostosis population.

Limitations of study

Due to the long-term retrospective study design, radiological data of 47 patients were missing. However, statistical analysis revealed that this attrition was not selective with respect to age, gender, craniosynostosis subgroup, or intelligence. In addition, because of low prevalences of the individual subtypes of craniosynostosis, we were not able to determine the risk of behavior problems in these separate groups. Although the sample size of this study was relatively high compared to previous studies, our subgroup analyses seemed to have suffered from low power due to the small number of patients for each subgroup.

CONCLUSION

When intelligence is taken into account, craniosynostosis is not associated with an increased risk of behavioral and emotional problems. Type of craniosynostosis and a beaten-copper pattern before the age of 18 months do not affect the risk of behavioral and emotional problems.

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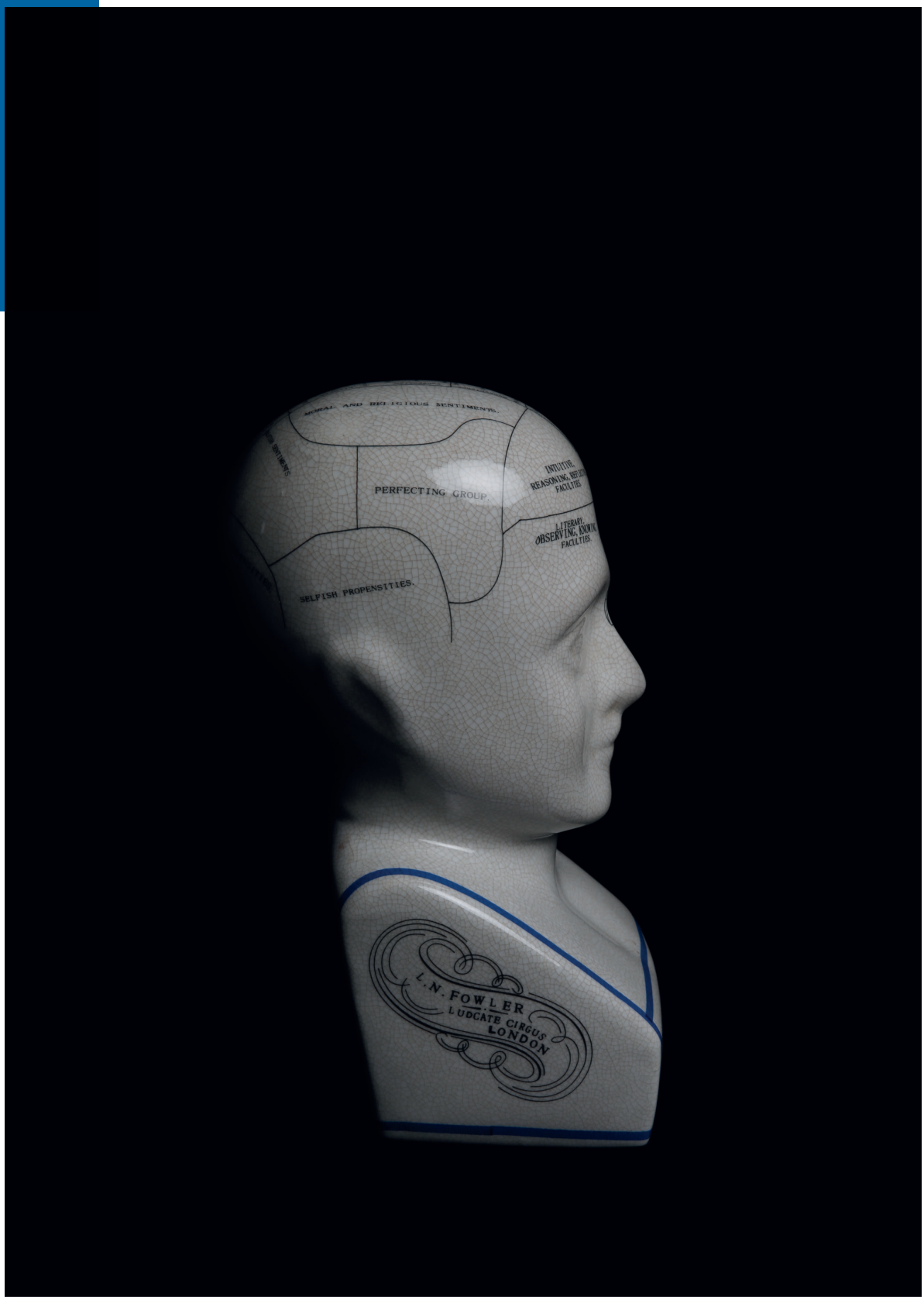
MORAL AND RELIGIOUS SENTIMENTS.
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CHAPTER 3

COGNITIVE AND BEHAVIORAL FUNCTIONING IN 82 PATIENTS WITH TRIGONOCEPHALY

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ABSTRACT

Background: The main objective was to assess the prevalence rates of attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder and features of autism spectrum disorders in trigonocephalic patients, using validated instruments and by ruling out the confounding influence of IQ. The second aim was to assess the association between extracranial anomalies and cognitive and/or behavioral problems in patients with trigonocephaly.

Methods: Objectives were studied in 82 trigonocephalic patients aged 2 to 18 years at the Erasmus Medical Center in Rotterdam, the Netherlands. Features of autism spectrum disorders were assessed using the Social Communication Questionnaire. Attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder were assessed with the Diagnostic Interview Schedule for Children–Parent Version. The presence and nature of extracranial anomalies was ascertained by a clinician.

Results: Mental retardation (IQ <70) was present in 9% of the patients with trigonocephaly. Findings indicated a 70% versus 24% prevalence of psychopathology (attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder and features of autism spectrum disorders) in patients with IQ levels of <85 and ⩾85, respectively. In the latter group, psychopathology was not significantly more common than expected based on prevalence rates reported in community samples. Extracranial anomalies were significantly correlated with lower IQ levels. However, when adjusted for IQ, the presence of extracranial malformations was not associated with an increased risk of behavioral problems.

Conclusion: The relatively high prevalence of behavioral problems in patients with trigonocephaly seems to be mainly attributable to the co-occurrence of trigonocephaly and low intelligence.

INTRODUCTION

Trigonocephaly is one of the most common forms of single suture craniosynostosis (van der Meulen et al., 2009). The typically wedge-shaped skull, when viewed from above, originates from a premature stenosis of the metopic suture followed by a bilateral growth restriction of the forehead (Figure 1). In a minority of patients, extracranial anomalies are present, such as finger deviations and/or extra digits, ear anomalies, maxillofacial abnormalities, or cardiac defects.

The literature shows a high prevalence of cognitive and/or behavioral problems in patients with trigonocephaly (Bottero, Lajeunie, Arnaud, Marchac & Renier, 1998; Kapp-Simon, 1998; Kelleher et al., 2006; Lajeunie, Le Merrer, Marchac & Renier, 1998; Shimoji, Shimabukuro, Sugama & Ochiai, 2002; Shimoji & Tomiyama, 2004; Sidoti, Marsh, Marty-Grames & Noetzel, 1996). Sidoti et al. (1996) for example reported that 33 percent of their sample of patients with trigonocephaly showed cognitive and/or behavioral problems, such as mental retardation (IQ <70), attention deficit/hyperactivity disorder and aggressive behavior. Kelleher et al. (2006) described a 37 percent prevalence of attention deficit/hyperactivity disorder and/or autism spectrum disorder in 63 patients with non-syndromic trigonocephaly. Bottero et al. (1998) reported that 31 percent of their sample of patients with trigonocephaly (n=76) showed cognitive problems (IQ <90) and/or behavioral problems. Patients with both trigonocephaly and extracranial anomalies seem to have an even higher risk of cognitive and behavioral problems when compared to those without extracranial anomalies (Bottero et al., 1998; Lajeunie et al., 1998).

Literature thus suggests that patients with trigonocephaly have an increased risk of mental retardation and psychopathology. However, the well-established link between mental retardation and psychopathology (Baker, Blacher, Crnic & Edelbrock, 2002; Dekker, Koot, van der Ende & Verhulst, 2002; Fergusson & Horwood, 1995; Hinshaw, 1992; King, State, Shah, Davanzo & Dykens, 1997; Rapport, Scanlan & Denney, 1999; State, King & Dykens, 1997) in combination with the relatively high incidence of mental retardation in trigonocephalic patients, suggests that (unlike previously reported) not trigonocephaly but mental retardation is associated with psychopathology in this patient group. So far, none of the studies on psychopathology in patients with trigonocephaly have considered the association between intelligence and psychopathology. In other words, it is still unclear if trigonocephaly is still associated with psychopathology when the influence of intelligence is accounted for. In addition, most previous studies on psychopathology in patients with trigonocephaly did not provide information about the instruments that were used to assess psychopathology, or did not use validated instruments. This makes judging the validity of their results difficult.

In the present study, we aimed to assess the prevalence of mental retardation, attention defi cit hyperactivity disorder, oppositional defiant disorder, conduct disorder, and features of autism spectrum disorders, in patients with trigonocephaly, using validated instruments and taking the association between low intelligence and psychopathology into account. Furthermore, we investigated whether having extracranial anomalies increases the risk of mental retardation and psychopathology in patients with trigonocephaly

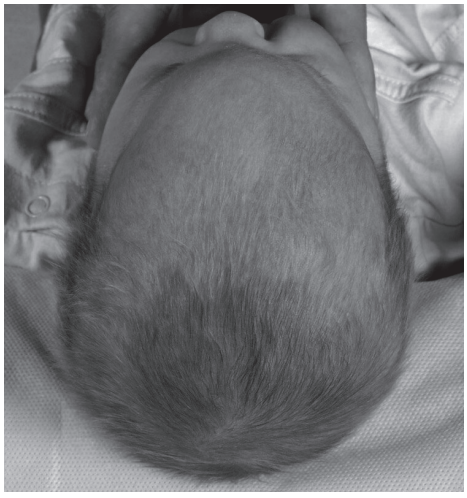

Figure 1. Trigonocephalic skull shape of a 6-month-old boy.

METHODS

Patient population

For this study, all patients were invited that had presented with metopic synostosis between 1990 and 2006 at the Dutch Craniofacial Center of the Erasmus University Medical Center in Rotterdam, The Netherlands. This center treats approximately 70 percent of all patients in the Netherlands referred for treatment with trigonocephaly (Kweldam, 2010). Of all patients, 94% (88 out of 94) agreed to participate in this study. Six patients did not participate because of limited access to transportation. Inclusion criteria for this study were: 1) a diagnosis of metopic synostosis confirmed on a three-dimensional computed tomographic scan, and 2) Dutch as the first language. Patients were excluded if they had other primary defects of morphogenesis which are associated with cognitive dysfunction, resulting in the exclusion of six patients that were diagnosed with focal temporal epilepsy (n=1), chromosome 9p deletion (n=2), Tetralogy of Fallot (n=1), Muenke syndrome (n=1), and 22q 11.2 deletion syndrome (n=1). The final sample consisted of 82 patients (68 male patients and 14 female patients),

ranging in age from 2 to 18 years at the time of inclusion. All patients included in this study had undergone fronto-supra-orbital remodeling and advancement operation at a mean age of 11 (SD 4) months, thus before the start of this study.

In all patients, the presence of any extracranial anomalies was determined by a clinician. Extracranial anomalies were identified in 26 percent of the included patients (see *Table* 1).

Table 1. Frequencies and percentages of extracranial anomalies, categorized following Bottero et al. (1998) (2).

Extracranial anomaly	n	%
Upper limb anomalies	10	38
Lower limb anomalies	4	15
Cardiac anomalies	6	23
Facial anomalies	5	19
Hearing impairment	1	4
1 extracranial anomaly	16	62
2 extracranial anomalies	5	38

MEASURES

Intelligence Quotient (IQ)

Depending on the age of the participant, intelligence was obtained with one of the four following intelligence tests. In 2-5 year old patients (n=21), IQ was assessed using the Dutch version (Willigen, 2002) of the Mullen Scales of Early Learning (Mullen, 1995). From the age of 5, intelligence was estimated using a four-subtest short form of the Dutch versions (Hendriksen J, 1997; Kort et al., 2005; Stinissen, Willems, Coetsier & Hulsman, 1970) of the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 2002), the Wechsler Intelligence Scale for Children (Wechsler, 1991) or the Wechsler Adult Intelligence Scale 3rd edition (Wechsler, 1997). In 5-7 year old children (n=27) the Wechsler Preschool and Primary Scale of Intelligence was used, for 7-16 year old patients (n=32) the Wechsler Intelligence Scale for Children was used and for patients older than 16 years (n=2) the Wechsler Adult Intelligence Scale was used. All these intelligence tests have a mean score of 100 and a standard deviation (SD) of 15. The four-subtest short forms of the intelligence scales we used can be extrapolated to full scale IQs (Kaufman, Kaufman & Mclean, 1994; Thompson, 1995; Tsushima, 1994).

Features of Autism Spectrum Disorders

The Dutch translation (Roeyers, Warreyn & Raymaekers, 2002) of the Social Communication Questionnaire (Rutter, Bailey & Lord, 2003) was used to assess features of autism spectrum disorders. The Social Communication Questionnaire contains 40 items based on the Autism Diagnostic Interview – Revised (Lord, Rutter & Le Couteur, 1994) that have been modified to be readily understandable by primary caregivers and that can be answered on a two-point scale (yes or no). Scores of 15 or more are considered deviant (Roeyers et al., 2002; Rutter et al., 2003), and will be referred to as autism spectrum disorders-features. The Social Communication Questionnaire has good reliability and validity (Roeyers et al., 2002; Rutter et al., 2003). The Social Communication Questionnaire scores of the patients with trigonocephaly were compared to those of school children from large studies conducted in the United Kingdom (UK) listed in *Table* 2 (Chandler et al., 2007; Mulligan, Richardson, Anney & Gill, 2008). Data on autism spectrum disorders-features were missing for 4 patients, resulting in a final sample of 78 for the analyses on autism spectrum disorders (mean age 7.1 years, SD 3.0).

Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder and Conduct Disorder

To assess attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder, the Dutch version of the Diagnostic Interview Schedule for Children – Parent Version 4th Edition was used (Ferdinand, van der Ende & Mesman, 1998). The Diagnostic Interview Schedule for Children is a highly structured diagnostic parental interview, designed to generate *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition diagnoses by ascertaining the presence or absence of symptoms. The Diagnostic Interview Schedule for Children includes 34 child and adolescent psychiatric diagnoses, which are arranged into six modules. Given the aims of the present study, we focussed on the module 'Disruptive Behavior Disorders'. This module requires a minimal age of 6 years of the child. Studies have demonstrated moderate to good test-retest reliability, and moderate to good agreement with evaluations by clinicians (Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000).

Diagnostic Interview Schedule for Children scores were used in two ways: 1) to compute correlations we used continuous scores, and 2) dichotomized scale scores were used to compute prevalences of *Diagnostic and Statistical Manual of Mental Disorders* diagnoses.

Epidemiological research (Canino, Polanczyk, Bauermeister, Rohde & Frick, 2010; Faraone, Sergeant, Gillberg & Biederman, 2003) has shown that the prevalences of attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorders are in the same range in many countries and that variability in prevalence was mostly related to methodological differences across studies. Therefore outcome prevalences of Diagnostic

Interview Schedule for Children diagnoses in our study were compared to prevalences of Diagnostic Interview Schedule for Children diagnoses in school/community samples from large studies conducted in the United States (Bird et al., 2006; Froehlich et al., 2007), shown in *Table 2*.

Because 25 patients had not yet reached the age of 6 years during the data collection period, the Diagnostic Interview Schedule for Children data are missing for this group. Another 2 patients were excluded from the analysis because of missing items, resulting in a final sample of 55 patients (mean age 8.2 years, SD 2.9) for analyses on attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorders.

Table 2. Prevalences of ASD-features, ADHD, ODD and CD in samples using the same instruments. If X2 analysis did not show significant difference between study samples, percentages where pooled.

	Author	Patients		Age range (mean age)	deviant/total n	%	Pooled %
ASD-features measured with the SCQ	Chandler 2007	936 subjects attending mainstream schools in a predominantly middle-income town in the southeastern United Kingdom		(12.0)	18/411	4.4	**3.7**
	Mulligan 2008	240 pupils from an Irish primary school of mixed gender		4-12 (8.14)	3/153	1.8	
ADHD measured with the DISC-IV-P	Froehlich 2007	representative sample of the US population from 2001 to 2004		8-11	119/1160	10.3	**10.3**
	Bird 2006	Community samples of	The south Bronx in New York City	5-13 (9,2)	79/1138	6.9	**7.0**
			Puerto Rico in San Juan	5-13 (9,2)	97/1353	7.2	
ODD measured with the DISC-IV-P	Bird 2006	Community samples of	The south Bronx in New York City	5-13 (9,2)	55/1138	4.8	**5.0**
			Puerto Rico in San Juan	5-13 (9,2)	70/1353	5.2	
CD measured with the DISC-IV-P	Bird 2006	Community samples of	The south Bronx in New York City	5-13 (9,2)	9/1138	0.8	**0.8**
			Puerto Rico in San Juan	5-13 (9,2)	10/1353	0.7	

Statistics

Analyses were conducted in three phases. First, we assessed the difference in the prevalences of mental retardation and borderline intellectual functioning between trigonocephalic patients and the general population by comparing proportions of patients with mental retardation with proportions of the general population according to the normal distribution of IQ, using binomial tests.

Second, Pearson's correlations were computed between IQ scores and the continuous scores on autism spectrum disorder-features, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder. Subsequently, prevalences of autism spectrum disorder-features, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder were determined using the dichotomized scale scores. Prevalences were computed for subgroups based on IQ; group 1, IQ <85 and group 2, IQ ⩾85. Differences between prevalences for group 2 and prevalences for community/school samples were tested with chi-square analysis (*Table 3).*

Third, partial correlation analyses were performed to assess the association of extracranial anomalies with continuous scores on autism spectrum disorder-features, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, adjusted for IQ.

RESULTS

Sample characteristics

Descriptive information on the outcome variables is provided in *Table 3*. Mean IQ of the sample was 101.3 (range 50-147; SD 21.0). Mental Retardation, defined as an IQ of 2 SD below the mean (IQ <70) (APA, 2001), was present in 9 percent (n=7) of the patients. This was significantly ($p<0.01$) higher compared to the expected 2.5 percent that is found in the general population according to the normal distribution. In contrast, borderline intellectual functioning (defined as having an IQ between 70 and 85) was present in 12 percent of the patients, which is not significantly different ($p>0.05$) from the expected 13.5 percent in the general population. Overall, mental retardation or borderline intellectual functioning (IQ <85) was present in 21 percent of the patients which is also not significantly different ($p >0.05$) from the expected 16 percent.

The prevalence of Social Communication Questionnaire scores in the deviant range was 14 percent, which indicates that 14 percent of the trigonocephaly sample presented with autistic features. When all trigonocephalic patients with information on the Diagnostic Interview Sched- ule for Children were considered (all patients ⩾ 6 years: n=55), the prevalence of

attention deficit hyperactivity disorder was 15 percent, the prevalence of oppositional defiant disorder was 20 percent, and the prevalence of conduct disorder was 4 percent.

When attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder were combined in a composite measure, 27 percent of the patient sample met the criteria for one of these diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. When low IQ (<85) and autism spectrum disorder-features were also included in this composite measure, 38 percent of the total sample had either autistic features and/or IQ <85 and/or met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition for attention deficit hyperactivity disorder, oppositional defiant disorder or conduct disorder.

Intelligence and features of Autism Spectrum Disorders

Correlations: A significant correlation between the continuous variables IQ and Social Communication Questionnaire-scores ($r=-0.46$; $p<0.001$) indicated that patients with lower IQ scores had more autistic features than patients with higher IQ scores.

Prevalences: When dichotomizing both IQ scores (IQ < 85 and IQ ⩾ 85) and Social Communication Questionnaire scores (normal range versus deviant range) our findings indicated autism spectrum disorder-features in 44 percent of the patients with IQ <85, and in 7 percent of the patients with IQ ⩾85. The latter prevalence did not significantly differ from the prevalence of autism spectrum disorder in community/school samples from the US. All group scores are shown in *Table 3*.

Intelligence and attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder

Correlations: The continuous variables IQ and attention deficit hyperactivity disorder score (Diagnostic Interview Schedule for Children) were significantly correlated ($r=-0.36$; $p<0.01$). Likewise, there was a significant correlation between IQ and oppositional defiant disorder ($r=-0.38$; $p<0.01$). This indicated that low IQ was associated with more attention deficit hyperactivity disorder and oppositional defiant disorder symptoms. There was no significant correlation between IQ and conduct disorder symptomatology ($r= -0.20$ $p> 0.05$).

Prevalences: Using dichotomized scores for IQ (IQ < 85 and IQ ⩾ 85) and attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder (*Diagnostic and Statistical Manual of Mental Disorders* classification, yes or no), the prevalences of attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder were 30, 60 and 10 percent, respectively, in the IQ ⩽85 group. In the group with IQ ⩾85 prevalences for attention deficit hyperactivity disorder, oppositional defiant disorder and conduct

disorder were 11, 11, and 2 percent, respectively. These latter prevalences did not differ significantly from those in community/school samples from the US (*Table 2*). The prevalence of oppositional defiant disorder was 11 percent, which indicated a trend (p=0.08) toward a higher prevalence of oppositional defiant disorder in these patients compared to the 5.0 percent in community/school samples from the US. Findings are presented in *Table 3*.

Extracranial anomalies in trigonocephaly

Group differences: Trigonocephalic patients with extracranial anomalies (n=21) had a mean IQ score of 92.7 (SD 21.2), which was significantly lower compared to the mean IQ score of trigonocephalic patients without extracranial anomalies (n=61) who had a mean IQ score of 104.2 (SD 20.3) (t=2.2; df=80; p<0.05). There was no significant correlation between the presence of one (mean IQ score= 92.56; SD=23.9) or two (mean IQ score 93.20; SD 10.1) extracranial anomalies and intelligence (r=-0.14; p=0.55).

Prevalences: Mental retardation was significantly more prevalent (chi-square=4.0; df=1; p<0.05) in trigonocephalic patients with extracranial anomalies (19 percent) compared to trigonocephalic patients without extracranial anomalies (5 percent). Findings are presented in *Table 3*.

Partial correlations: When intelligence was taken into account, no significant correlations were found between the absence or presence of extracranial anomalies and autism spectrum disorder-features, (r=-0.02; P>0.05), attention deficit hyperactivity disorder (r=0.04; p>0.05), oppositional defiant disorder (r=-0.18; p>0.05), or conduct disorder (r=-0.15; p>0.05).

Table 3. Frequencies and prevalences of psychopathology in trigonocephalic patients versus the general population measured with the same instruments.

	Total sample	Trigonocephaly IQ≥85			Trigonocephaly IQ<85			Community/school sample(s)
	% /(n)	*% /(n)*			*% /(n)*			*% (*)*
		combined	*with ‡*	*without ‡*	*combined*	*with ‡*	*without ‡*	
ASD-features ***(SCQ>15)***	**14** (11/78)	**6** (4/62)	**20** (3/15)	**2** (1/47)	**44** (7/16)	**40** (2/5)	**45** (5/11)	**3.7** (p=0.30)
ADHD ***(DSM-IV criteria)***	**15** (8/55)	**11** (5/45)	**20** (2/10)	**9** (3/35)	**30** (3/10)	**25** (1/4)	**33** (2/6)	**7.0 - 10** (p=0.37 - p=0.80)
ODD ***(DSM-IV criteria)***	**20** (11/55)	**11** (5/45)	**0** (0/10)	**14** (5/35)	**60** (6/10)	**25** (1/4)	**83** (5/6)	**5.0** (p=0.08)
CD ***(DSM-IV criteria)***	**4** (2/55)	**2** (1/45)	**0** (0/10)	**3** (1/35)	**10** (1/10)	**0** (0/4)	**17** (1/6)	**0.8** (p=0.30)
Psychopathology (ASD-features, ADHD, ODD, CD)	**33** (18/55)	**24** (11/45)	**30** (3/10)	**23** (8/35)	**70** (7/10)	**50** (2/4)	**83** (5/6)	**-**
Psychopathology and/or low IQ (below 85)	**38** (21/55)							

‡ extracranial anomalies

* Between-group comparison of prevalence rates of ASD-features (SCQ > 15), ADHD-, ODD- and CD-diagnoses using X^2 analysis, comparing community sample(s) (*Table 2)* with trigonocephaly patients (IQ>85).

DISCUSSION

Intelligence and trigonocephaly

The prevalence of mental retardation in our study group of patients with trigonocephaly was 9 percent, which is significantly higher ($p<0.01$) than the 2.5 percent reported in the general population. Previous publications on intelligence levels in trigonocephalic patients have reported on comparable prevalences of mental retardation (between 10 and 13 percent) (Lajeunie et al., 1998; Sidoti et al., 1996).

Furthermore, our findings showed that mental retardation is particularly more common among trigonocephalic patients with extracranial anomalies. Mental retardation was present in 19 percent of the patients with extracranial anomalies versus 5 percent in patients without extracranial anomalies. In their review of 273 trigonocepaly patients, Lajeune et al. (1998) also reported a higher incidence of mental retardation in patients with extracranial anomalies (i.e. 34 percent versus 0.5 percent in trigonocephalic patients without extracranial anomalies).

Psychopathology in trigonocephaly

The present study aimed to determine the prevalence rates of autism spectrum disorder-features, attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder in patients with trigonocephaly, while taking intelligence into account. Therefore, we stratified the sample into two groups; IQ less than 85 and IQ greater or equal to 85. Our findings indicate a 70 percent versus 24 percent prevalence of psychopathology (autism spectrum disorder-score in the deviant range, attention deficit hyperactivity disorder, oppositional defiant disorder or conduct disorder diagnoses) in patients with IQ less than 85 and IQ greater or equal to 85, respectively. Thus, psychopathology was more common in patients with IQ less than 85 than in patients with IQ greater or equal to 85. Among trigonocephalic patients with IQ levels greater or equal to 85, prevalence rates of autism spectrum disorder-features, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder were not significantly different compared to community/school samples of the US or UK (Bird et al., 2006; Chandler et al., 2007; Froehlich et al., 2007; Mulligan et al., 2008) (*Table 3)*. The trend ($p=0.08$) toward a higher prevalence of oppositional defiant disorder in our study is probably the result of the large proportion of boys in our sample (83 percent). Male sex is a risk factor for developing oppositional defiant disorder (Carlson, Tamm & Gaub, 1997; Rey, 1993) and therefore, will probably overestimate the prevalence of oppositional defiant disorder in our study sample.

Our results confirm the previously established association between IQ and psychopathology (Baker et al., 2002; Dekker et al., 2002; Fergusson & Horwood, 1995; Hinshaw, 1992; King et al., 1997; Rapport et al., 1999; State et al., 1997). This association, in combination with finding no significant link between trigonocephaly and psychopathology in patients with intelligence levels of 85 and above, suggests that the relatively high prevalence rates of autism spectrum disorder-features, attention deficit hyperactivity disorder, and oppositional defiant disorder in trigonocephalic patients are attributable to the increased likelihood of low intelligence levels in this group.

Extracranial anomalies in trigonocephaly

Twenty-six percent of the patients (n=21) in our sample presented with extracranial anomalies. Our findings indicate that, when IQ was taken into account, there is no significant correlation between the presence of extracranial anomalies and psychopathology. The presence of extracranial anomalies was associated with lower intelligence levels and an increased risk of mental retardation. Additional extracranial anomalies might reflect a higher level of constitutional abnormalities in patients with craniosynostosis, which might also be expressed in low intelligence levels and mental retardation. Given the absence of a significant correlation between the number of extracranial anomalies and intelligence, our results do not suggest that the degree of constitutional abnormalities is related to cognitive functioning. However, since our sample of patients with extracranial anomalies was very small, this finding should be interpreted with care. Future research should address this issue.

Brain pathology and trigonocephaly

Although the results from this study do not permit any inferences about the mechanism(s) underlying the association between trigonocephaly and mental retardation, several hypotheses have been proposed to explain this link. One of the most discussed hypotheses is that trigonocephalic patients suffer from increased intracranial pressure that causes neurodevelopmental damage of cerebral tissue by compromising neuronal oxygenation (Renier & Marchac, 1988). However, studies addressing this hypothesis showed (Arnaud, Renier & Marchac, 1995; Gewalli et al., 2001; Inagaki et al., 2007; Shimoji & Tomiyama, 2004; Siddiqi et al., 1995) contradictory results and were hampered by methodological problems, leaving the role of intracranial pressure on neurodevelopment in trigonocephalic patients unclear.

An alternative hypothesis is offered by Speltz et al. (2004), who proposed the "secondary cerebral deformation hypothesis". According to this hypothesis, growing cortical and even subcortical brain tissue is believed to be compressed or "redirected" within a skull that has

limited capacity to accommodate such growth, resulting in neurodevelopmental disorders. However, the finding that trigonocephalic patients with extracranial anomalies, in whom cognitive and behavioral problems are more common, did not have a more severe degree of frontal stenosis compared to patients without extracranial anomalies makes the "secondary cerebral deformating hypothesis" less likely (Bottero et al., 1998). A second alternative is proposed by Kjaer (1995), who suggested that the central nervous system and craniofacial skeleton are developmentally interconnected. Indeed, the fibroblastic growth factor receptors which play a role in the development of both the skull (Gripp, Zackai & Stolle, 2000; Kan et al., 2002) and the underlying brain have been found to play a role in craniosynostosis (Belluardo et al., 1997; Oh et al., 2003; Sleptsova-Friedrich et al., 2001; Wilke, Gubbels, Schwartz & Richman, 1997). This makes a hypothesis on interconnected deviant development of the skull and the brain, causing both craniosynostosis and cognitive and/or behavioral problems, plausible. Future research should further address the mechanism(s) behind cognitive and behavioral problems in patients with trigonocephaly.

Limitations

Although we present one of the largest samples of patients with trigonocephaly in the world, the absolute number of participants in this study was relatively small. Particularly our subgroup analyses seem to have suffered from low power due to the small number of patients in each subgroup. This might have hampered the detection of more subtle differences in psychopathology between trigonocephalic patients with average and high levels of cognitive functioning and normative individuals. Second, all patients included in the present study had undergone fronto-supra-orbital remodellation and advancement surgery, aimed at minimizing the development of high intracranial pressure (Eide & Fremming, 2003; Tamburrini, Caldarelli, Massimi, Santini & Di Rocco, 2005). Although it has not been demonstrated that this specific surgical procedure might affect cognitive functioning, we cannot exclude the possibility that this surgical intervention has affected the results of this study. Third, although the results of this study indicate that psychopathology is more common among trigonocephalic patients with mental retardation, the design of this study does not permit us to draw any conclusions about causation. Lastly, because previous research showed mostly disruptive behavior disorders in these patients, we have focused on this type of behavior disorders. Therefore, we cannot extrapolate the results of this study to other forms of psychopathology.

CONCLUSION

Based on the findings of the present study, the relatively high prevalence of autism spectrum disorder-features, attention deficit hyperactivity disorder, and oppositional defiant disorder in patients with trigonocephaly seems to be attributable mainly to the co-occurrence of trigonocephaly and low intelligence.

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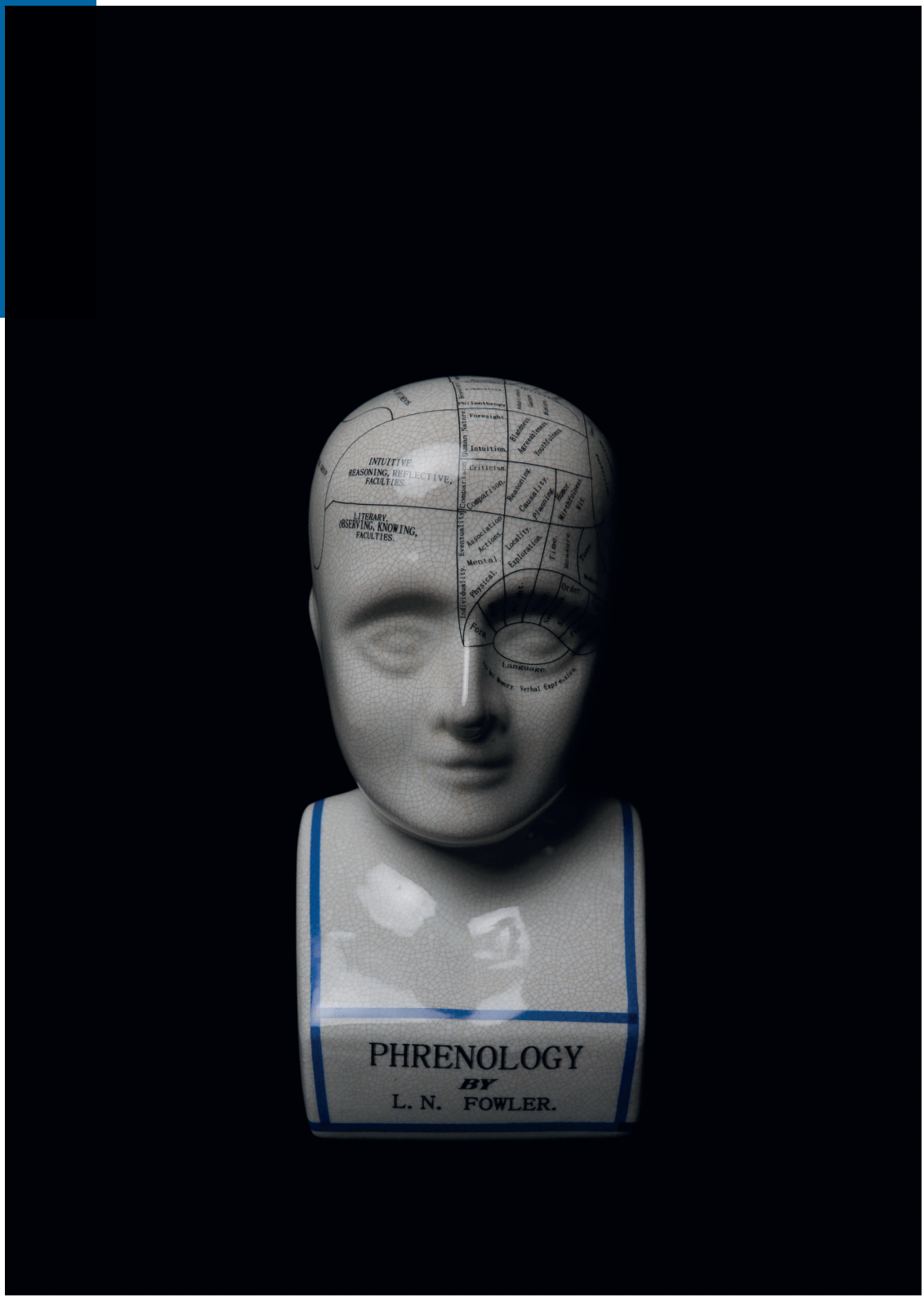
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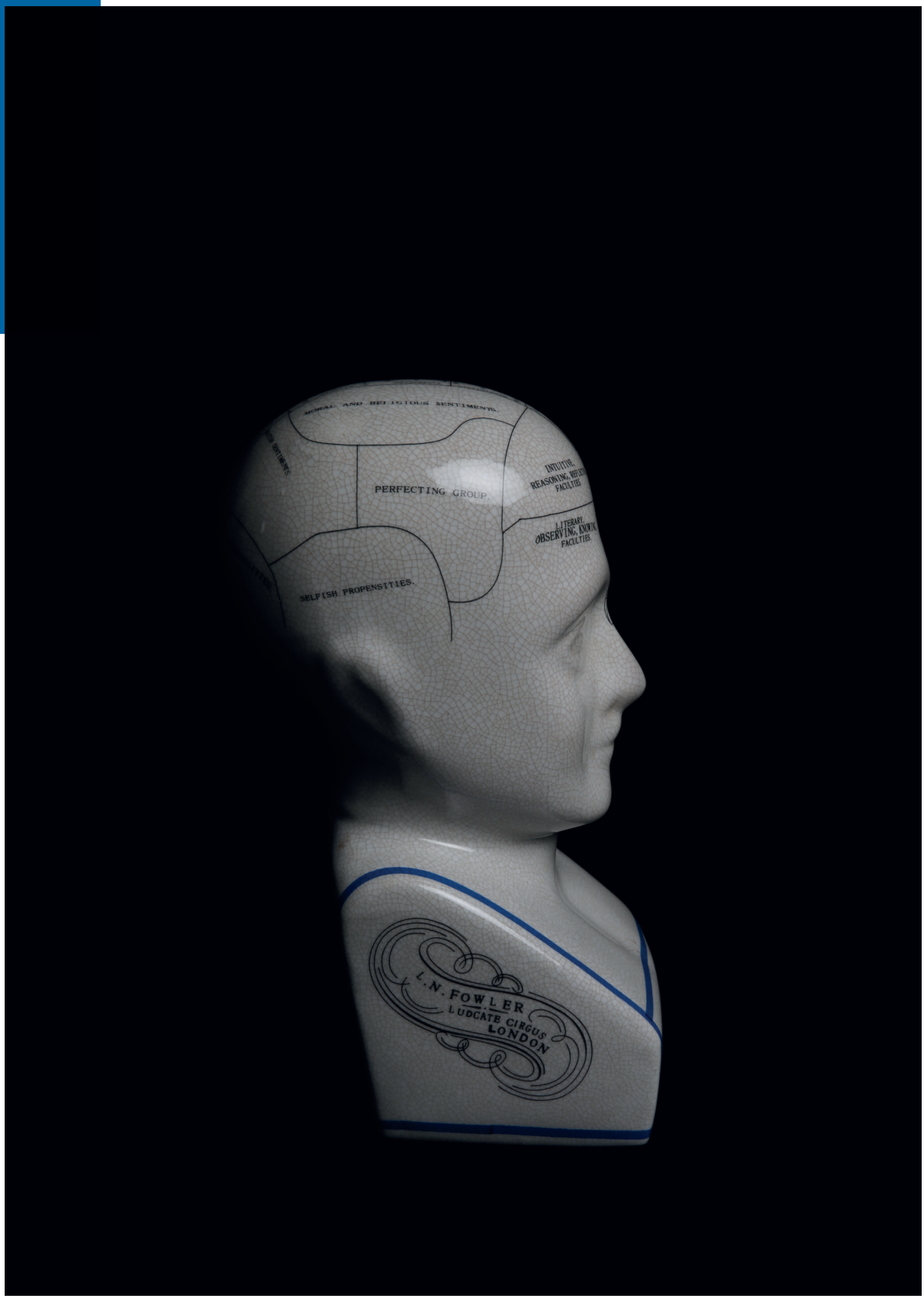
PART II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CHAPTER 4

EARLY BEATEN-COPPER PATTERN: ITS LONG-TERM EFFECT ON INTELLIGENCE QUOTIENTS IN 95 CHILDREN WITH CRANIOSYNOSTOSIS

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Joris J.B. van der Vlugt
Jolanda M.E. Okkerse
Bert Hofman

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ABSTRACT

Object: The aim of this study was to analyze the presence of beaten-copper patterns (BCPs) in children with craniosynostosis before 18 months of age and its association with their IQ at a later age.

Methods: The authors conducted a retrospective analysis of 538 cephalograms (obtained at a mean patient age of 1.16 years) from 95 patients. The BCP location and percentage of brain surface area covered were related to patient IQ scores obtained by the same psychologist using the Snijders–Oomen Nonverbal Intelligence Test–Revised, 51/2–17, and the Wechsler Preschool and Primary Scale of Intelligence–Revised.

Results: As much as 71.6% of patients presented with a BCP before 18 months of age (mean surface area of BCP 20.3%, 93% of patients presented with bilateral BCPs). The mean IQ was 95 ± 21.3 (range 50–136) at a mean patient age of 8.4 ± 2.59 years. There was a significant increase in the surface area covered by BCPs in the first 3 years of life ($p < 0.001$) and a significant difference in IQs between syndromic (30 cases, mean IQ 88.9) and nonsyndromic craniosynostosis cases (54 cases, mean IQ 98.9, $p = 0.03$). No significant correlation was found between IQ and the appearance of BCPs on presurgery radiographs (Pearson correlation coefficient = 0.143, $p = 0.19$) or their location (Spearman rank correlation coefficient = 0.091, $p = 0.45$). The BCPs appeared predominantly in the occipital region (41.1%).

Conclusions: Although the radiographic appearance of a BCP before the age of 18 months is an uncommon finding in healthy children, a craniosynostosis study group showed a preoperative BCP incidence of 71.6% and an increased incidence during the period of rapid brain expansion in the first 3 years of life. Note, however, that the presence of such a pattern had no significant long-term effect on patient intelligence levels. (DOI: 10.3171/PED-08/01/025)

INTRODUCTION

Craniosynostosis is the premature fusion of the cranial bone sutures. If untreated, it can lead to a reduced intracranial volume with the risk of elevated ICP. Intracranial pressure levels of 13–20% (Eide, Helseth, Due-Tonnessen & Lundar, 2002; Gault, Renier, Marchac & Jones, 1992; Tamburrini, Caldarelli, Massimi, Santini & Di Rocco, 2005) in single-suture synostosis and up to 30–40% in complex synostosis (Pijpers et al., 2004; Renier, 1989; Renier, Sainte-Rose, Marchac & Hirsch, 1982; Tamburrini et al., 2005) have been reported. Several authors have commented on the correlation between craniosynostosis and diminished intelligence (Arnaud, Renier & Marchac, 1995; Courchesne et al., 2000; Renier, 1989; Renier & Marchac, 1987; Renier et al., 1982), reporting a lower than average IQ in a nonsurgically treated population and the prevention of regressing intelligence levels by corrective surgery performed before the age of 12 months. (Arnaud et al., 2002; Arnaud et al., 1995; Bottero, Lajeunie, Arnaud, Marchac & Renier, 1998; Da Costa et al., 2006; Renier, 1989; Renier & Marchac, 1987; Renier et al., 1982). Although not all authors have supported these findings, a significant correlation with impaired neuropsychological development seems to be undisputed. (Kapp-Simon, 1994, 1998; Kapp-Simon, Figueroa, Jocher & Schafer, 1993; Kapp-Simon, Leroux, Cunningham & Speltz, 2005; Magge, Westerveld, Pruzinsky & Persing, 2002; Speltz, Kapp-Simon, Cunningham, Marsh & Dawson, 2004). Reading and/or spelling learning disabilities have been described in up to 50% of children with single suture craniosynostosis (Endriga & Kapp-Simon, 1999; Kapp-Simon, 1998; Magge et al., 2002), a 3- to 5-fold increase in the risk for such disabilities compared with their occurrence in healthy individuals. (Speltz et al., 2004) Beaten-copper patterns, also known as “digital impressions” or “convolutional digitations” are frequently seen on skull radiographs obtained in patients with craniosynostosis (Fig. 1). (Bristol, Lekovic & Rekate, 2004; Guimaraes-Ferreira et al., 2001; Tamburrini et al., 2005; Tuite et al., 1996). It is tempting to interpret these findings as a sign of elevated ICP because they seem to roughly correspond to the gyral pattern of the underlying brain (Fig. 2).(Vignaud-Pasquier, Lichtenberg, Laval-Jeantet, Larroche & Bernard, 1964). In Davidoff’s (Davidoff, 1936) classic review of 2500 cranial radiographs, however, BCPs were shown to be common and related to age in patients older than 18 months of age but uncommon in those younger than 18 months. Thus, the appearance of a BCP on radiographs became accepted as an indicator of normal brain growth in children. The persistently high incidence of BCPs in patients with craniofacial issues, often before the age of 18 months, has fueled further speculation. For instance, it remains unclear what role, if any, ICP plays in the evolution of a BCP. (Bristol et al., 2004; Eide et al., 2002; Greene, 1998; Guimaraes-Ferreira et al., 2001). Even though the incidence of these patterns is the same after the age of 18 months in the normal growing population,

Tuite et al. (1996) noted a more severe and more generally located presence in patients with craniofacial problems. These authors reported a correlation between generalized BCPs and significantly higher ICPs. Furthermore, the incidence of a BCP is known to be higher in children with complex craniosynostosis, which is associated with a greater incidence and a higher level of elevated ICP, when compared with those in the single-suture synostosis population as mentioned above. (Greene, 1998; Tamburrini et al., 2005; Thompson, Malcolm, Jones, Harkness & Hayward, 1995; Tuite et al., 1996). Many studies have focused on the correlation between ICP and IQ in patients with craniosynostosis. (Abe, Ikota, Akino, Kitami & Tsuru, 1985; Arnaud et al., 2002; Bartels, Vaandrager, de Jong & Simonsz, 2004; Bottero et al., 1998; Bristol et al., 2004; Cohen et al., 2004; Da Costa et al., 2006; Renier, 1989; Renier, Cinalli, Lajeunie, Arnaud & Marchac, 1997; Renier, Lajeunie, Arnaud & Marchac, 2000; Renier & Marchac, 1987; Renier et al., 1982; Thompson et al., 1995). Moreover, several authors have also addressed the link between ICP and the BCP, (Bristol et al., 2004; Eide et al., 2002; Greene, 1998; Guimaraes-Ferreira et al., 2001; Tuite et al., 1996) although none has taken into account the long-term developmental effect of having a BCP at an early age. In the present study, we attempted to address this deficiency by relating the presence of a BCP before the age of 18 months to the IQ of these children with craniosynostosis at a later age. Because the appearance of a BCP before that age seems to be specific to craniosynostosis, the ability to predict the long-term outcome of IQ based on the presence and severity of a BCP on lateral cranial radiographs at presentation of craniosynostosis (usually before the age of 18 months) may prove diagnostically valuable.

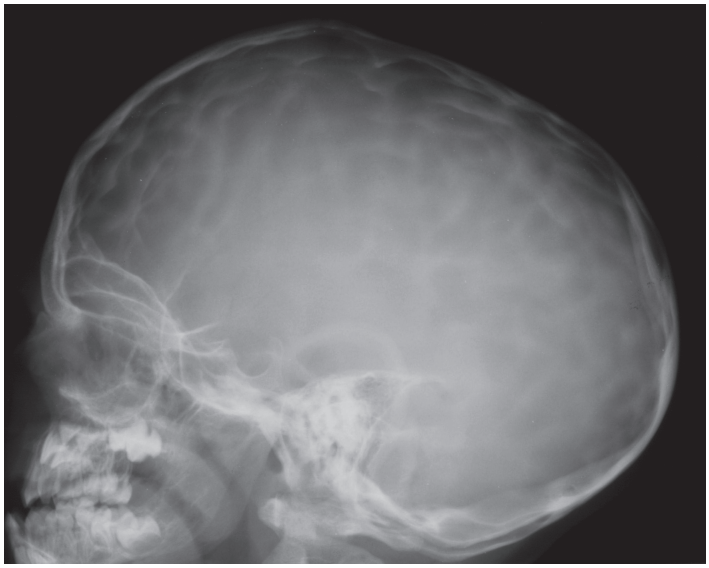

Figure 1. Generalised beaten copper pattern as seen on a lateral cephalogram

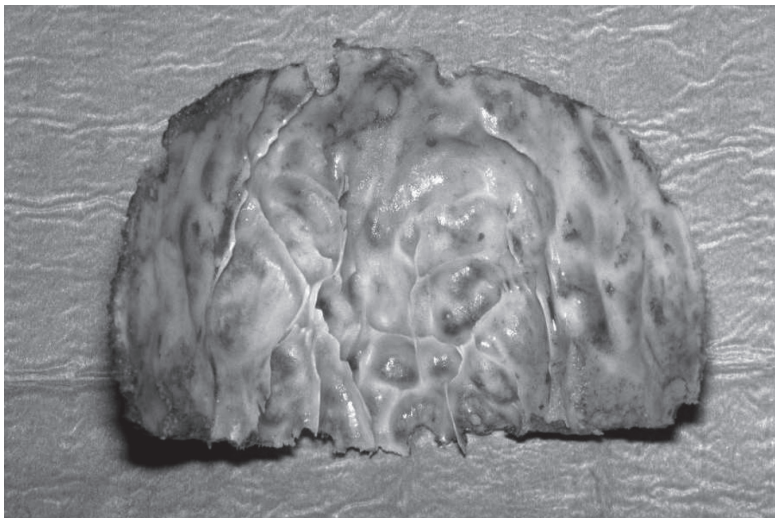

Figure 2. Generalized beaten-copper patterns seen on a frontal bone that was extracted during cranial vault surgery

CLINICAL MATERIAL AND METHODS

Patient Population

The population of interest consisted of 138 patients (83 males and 55 females) presenting with primary craniosynostosis at the Erasmus Medical Center in Rotterdam, The Netherlands. The children considered for inclusion in this study were born between 1978 and 1992. Forty-three of the patients were excluded from analysis because of missing radiographic records, leaving 95 patients available for the study (Table 1). All patients underwent cranial expansion, with the method depending on the location and number of sutures involved.

Table 1. Range and frequency of diagnosis, n = 95

Craniosynostosis	Type	Frequency	%
Non syndromic, single suture	Scaphocephaly	24	25,3
(n= 50, 53%)	Plagiocaphaly	20	21,1
	Plagiocephaly (occ)	1	1,1
	Trigonocephaly	5	5,3
Non syndromic, multiple sutures	Brachycephaly	6	6,3
(n= 8, 8%)	Complex craniosynostose	1	1,1
	Oxycephaly	1	1,1
Syndromic	Apert syndrome	8	8,4
	Carpenter syndrome	2	2,1
	Cohen syndrome	1	1,1
	Crouzon syndrome	12	12,6
	Pfeiffer syndrome	2	2,1
	Saethre-Chotzen	10	10,5
Missing diagnosis		2	2,1
Total		**95**	**100**

DATA COLLECTION

The 538 cranial radiographs (lateral and frontal views) in these 95 patients were digitized, and later evaluated by two independent investigators using Image J software (Wayne Rasband, National Institutes of Mental Health; Fig. 3). Frontal views were evaluated to determine whether the BCPs were evenly distributed over both cranial halves, and the percentage of brain area covered by the BCPs were divided in two if the pattern appeared on only one side of the skull. The patterns were quantified using the lateral radiographs; the total intracranial volume (A in Fig. 3 left) and the area in which the pattern appeared (B in Fig. 3 right) were delineated, and the software program was used to compare the two sets of pixels, resulting in a percentage. Each measurement was done twice; when the difference between the percentages calculated by each observers was < 10%, the mean of the two was used in the analysis. When the difference was > 10%, a consensus was reached after a joint review by both observers. Patient IQs were obtained by a psychologist using the Snijders–Oomen Nonverbal Intelligence Test–Revised, 51/2–17 (Snijders, Tellegen & Laros, 1988) and the Wechsler Preschool and Primary Scale of Intelligence–Revised (Wechsler, 2002) (both with a mean score ± standard deviation of 100 ± 15).

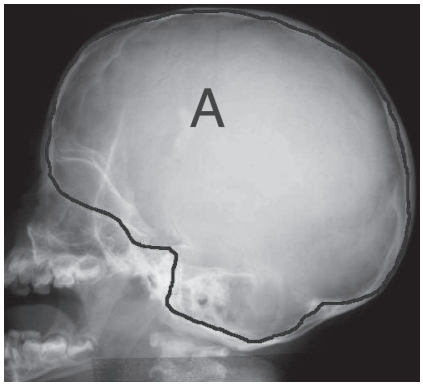

Figure 3a. Total intracranial area as marked on lateral cephalogram

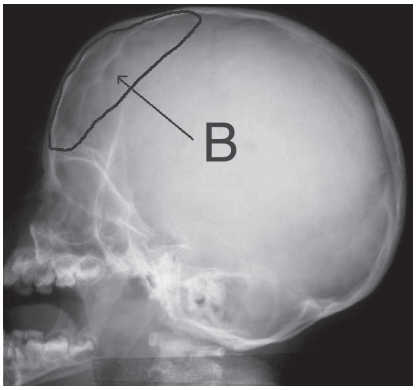

Figure 3b. Intracranial area marked as beaten copper pattern (area B/A x 100% = 9,8% BCP in this case)

DATA ANALYSIS

Patient IQs were compared with respect to the incidence and location of BCPs. The difference between nonsyndromic and syndromic craniosynostosis in terms of the incidence of BCP and the IQs were taken into account. The location of BCPs on lateral radiographs was categorized according to the following anatomical regions: frontal, parietal, occipital, and frontal and

occipital combined. The data were examined for correlations between patient age and the prevalence of BCPs.

STATISTICAL ANALYSIS

An analysis of missing values was conducted using chi-square and t-tests and by evaluating the results of target analyses. Reliability was tested using an intraclass correlation in which 0.70 was considered to be the critical value. Statistical comparisons were performed using the Spearman rank correlation coefficient, and probability values < 0.05 were considered statistically significant. The correlation between patient age and the percentage of BCPs was calculated using a mixed-model analysis.

RESULTS

Presurgical radiographs were obtained on initial presentation in the 95 patients at a mean age of 1.16 ± 1.93 years (range 1 day–12.5 years). It was found that 71.6% of the children presented with an already apparent BCP within the first 18 months of life. The mean surface area of the BCP in this presurgery group was 20.3%. All children underwent corrective surgery at a mean age of 1.85 ± 2.57 years (range 0.04–13.33 years). Intelligence tests were administered at a mean patient age of 8.4 ± 2.59 years (range 5.2–15.6 years). The mean IQ in the tested patients was 95 ± 21.3 (range 50–136). There was a significant difference in patient IQs in syndromic (30 cases, mean IQ 88.9) compared with nonsyndromic craniosynostosis cases (54 cases, mean IQ 98.9, p = 0.03; Fig. 4). Eleven patients did not undergo an IQ test. There was also a significant difference in the percentage surface area covered by BCPs between syndromic (35 cases, mean percentage 32.2%) and nonsyndromic craniosynostosis cases (58 cases, mean percentage 12.8%, p = 0.006). Records were missing in two patients, and thus, a diagnosis could not be rendered. Note, however, that no significant correlation was found between IQ and the appearance of BCPs on the presurgery radiographs (p = 0.19). The location of BCPs did not appear to have any influence on intelligence level at a later age (p = 0.45). The patterns appeared predominantly in the occipital region (41.1%; Fig. 5). Appearances in two or more locations combined (frontal, parietal, and occipital) were common. No correlation was seen between the location of the BCP and whether a child had the syndromic or nonsyndromic form of craniosynostosis.

Taking into account all 269 lateral radiographs, there was a significant annual increase (16%) in the brain surface area covered by BCPs between 0 and 3 years of age (p < 0.001), followed by a significant annual decrease (6%) after 7 years of age (p < 0.001; Fig. 6). Frontal

view analysis revealed a bilateral (symmetrical) appearance of patterns in 93% of cases. Six of 20 patients with plagiocephaly presented with a unilateral frontoparietal BCP only on the side of the affected suture. There was no significant difference with regard to age ($p = 0.25$), sex ($p = 0.75$), diagnosis ($p = 0.95$), IQ ($p = 0.99$), or age at the time of surgery ($p = 0.46$) between the excluded and included patient study groups. The mean difference between the two observers in their assessment of the percentage of brain surface area covered by BCPs was 1.0%. The interclass correlation coefficient determined to evaluate the interobserver variability was found to be sufficient at 0.83.

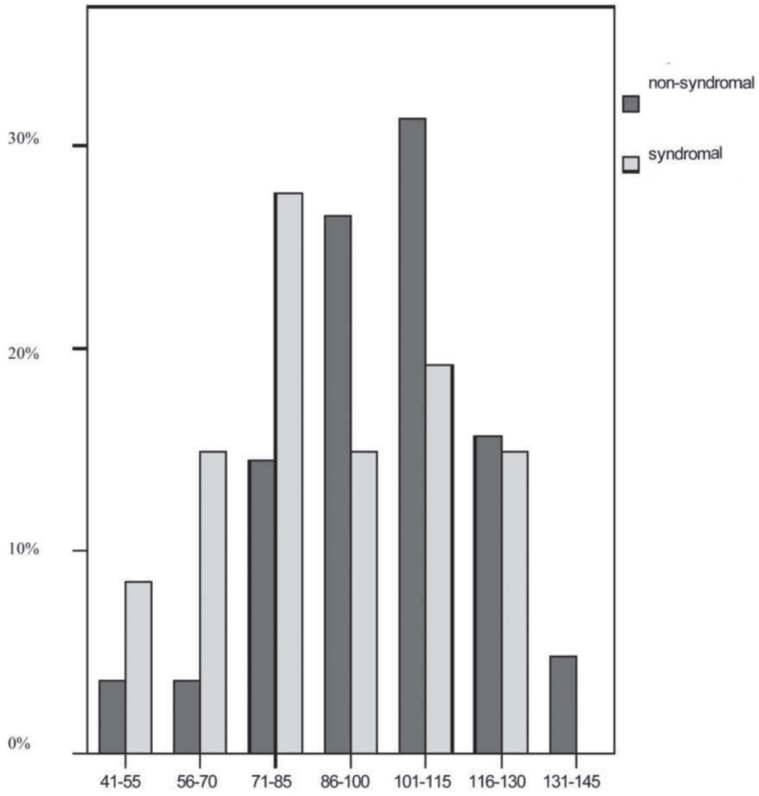

Figure 4 IQ distribution in syndromal and non-syndromal cases

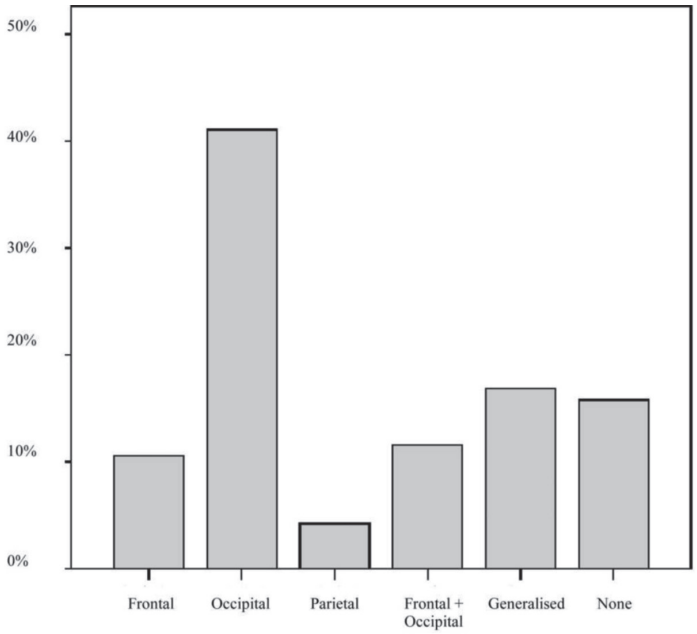

Figure 5. Percentage of beaten copper pattern per location as seen on lateral skull radiographs

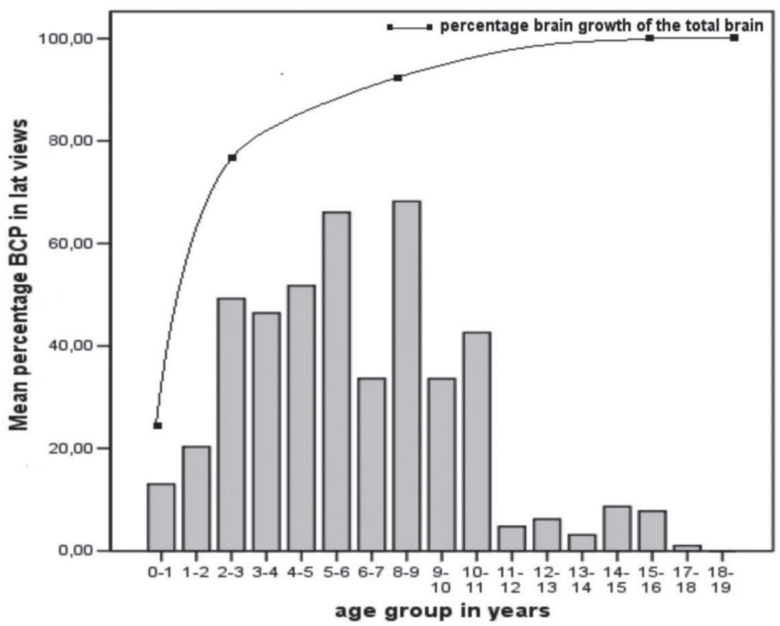

Figure 6. Spreading pattern of beaten copper patterns percentages over the years compared to the growthrate of the brain

DISCUSSION

Beaten-Copper Pattern

The radiographic presence of a BCP is considered to be a normal sign of the growing skull in older children but is not commonly seen before the age of 18 months. (Davidoff, 1936). Although the intracranial volume in craniosynostosis follows normal circumferential expansion rates given the compensatory growth of unaffected cranial sutures, (Gault et al., 1992; Virchow, 1851) just more than 70% of the children in our study group presented with BCPs before the age of 18 months. There was a significant relation between patient age and percentage of brain surface area covered by BCPs. The study population followed an equal spreading pattern similar to that seen in the normal population, as reported by Davidoff (1936). Remarkably, this equal spreading pattern seems to coincide with the pattern of normal brain growth in which the brain is 25–33% of its total volume at the end of the 1st year of life, followed by a period of rapid volume expansion resulting in a threefold increase by the age of 3 years (75% of its final volume). (Behrman, 2002; Courchesne et al., 2000). During this particular period a highly significant 16% yearly increase in the area covered by BCPs was seen in our study population ($p < 0.001$). Note, however, that there was no significant change in the succeeding 4 years. In this period, the growth rate of the brain slows down, and the brain reaches 90% of its final volume at the age of 7 years. (Behrman, 2002; Courchesne et al., 2000). After this age a significant regression in the area covered by BCPs has been noted. The last 10% of the brain volume is slowly accumulated over the following 11 years. In this same period a significant annual decrease in BCP surface areas of 6% was observed ($p < 0.001$; Fig. 6). These findings show a normal brain growth pattern in our patients with craniosynostosis. The significant age-related increases in BCPs, which appear during periods of rapid brain expansion, suggest a connection between the growth rate of the brain and the skull's limited ability to adjust accordingly. The relatively high percentage of unilateral BCPs in the group with plagiocephaly (in 30% of these 20 cases, the BCPs appeared only frontally on the affected side) also supports the theory that these BCPs are pressure related, as asserted by Tuite et al. (1996). Furthermore, the difference in the average BCP surface area at presentation between nonsyndromic (12.8%) and syndromic (32.2%) cases shows that skull growth in syndromic children is even more impaired.

Intracranial Pressure and BCP

Clinicians often use sequential radiographs to screen for elevated ICP in their treatment of patients with craniofacial disorders. Although the different radiographic signs are highly specific, Tuite et al. (1996) found radiography to have a low sensitivity for this particular

purpose. However, these authors noted a significant relation between the radiographic presence of a (generalized) BCP and elevated ICP. They asserted that the presence of diffuse BCPs, obliteration of the anterior sulci, or narrowing of the basal cisterns in children younger than 18 months predicted elevated ICP in more than 95% of cases. Other radiographic signs such as erosion of the sella and diastasis of the cranial sutures were at least 90% specific for elevated ICP in all age groups. Despite these correlations, they recommended not relying solely on radiography to reveal elevated ICP because of the universally low sensitivity of this imaging method.

Intracranial Pressure and IQ

The negative correlation between elevated ICP and reduced IQ in craniosynostosis has been well established (Arnaud et al., 2002; Bottero et al., 1998; Bristol et al., 2004; Cohen et al., 2004; Da Costa et al., 2006). The beneficial effects of corrective surgery in preventing the leveling off of IQs have also been described (Arnaud et al., 2002; Arnaud et al., 1995). Cohen and associates (2004) reported mild delays in the mental and psychomotor development index preoperatively in children with single-suture synostosis. Surgery improved psychomotor but not mental development. On the other hand, other authors have stated that single-suture synostosis is not associated with neurodevelopmental deficits in the early years of life (Kapp-Simon, 1994; Renier et al., 1982). Note, however, that in elder children, learning disabilities were seen in up to 50% of cases. (Kapp-Simon, 1998; Kapp-Simon et al., 1993; Kapp-Simon et al., 2005; Magge et al., 2002). It seems logical to expect a developmental impairment in the long term due to prolonged ICP elevation during the 1st years of rapid brain growth, although there are no data on how high the ICP should be and how long it should exist before these neurodevelopmental impairments arise.

Beaten-Copper Patterns and IQ

If a generalized BCP that is present before the age of 18 months is 95% specific for the presence of elevated ICP (Tuite et al., 1996) and if elevated ICP is related to a reduced IQ in craniosynostosis, (Renier, 1989; Renier, Sainte-Rose, Marchac & Hirsch, 1982), then what would be the relation between the early presence of a BCP and IQ at a later age in a population with craniosynostosis? Can one predict the level of IQ at a later age by reviewing the presence and level of BCPs on sequential radiographs over time? With more than 70% of the children in our craniofacial study group presenting with a BCP before the age of 18 months, this rate was significantly higher than normal. Note, however, that our statistical analysis showed no correlation between the presence of a BCP before surgery (usually performed before the age of 18 months) and a reduced IQ at a later age. This outcome was

true for both nonsyndromic and syndromic cases. Even though the BCP was seen mostly in the occipital region of the skull (41%), we found no significant correlation between the location of the patterns and IQ at a later age. Thus, IQ cannot be predicted by analyzing the BCPs on early cranial radiographs. The lack of a significant long-term effect on IQ in children with such apparent radiographic signs of ICP might be explained by the increased plasticity of the developing brain. (Boatman et al., 1999; Johnston, 2004). On the other hand, the IQ tests used to determine any neurodevelopmental effects just might not be sensitive enough to measure such effects. A high incidence of other, more sensitive neurodevelopmental impairments, such as reading and/or spelling learning disabilities in craniosynostosis, support this theory. (Endriga & Kapp-Simon, 1999; Kapp-Simon, 1998; Magge et al., 2002).

The Chicken or the Egg?

Other theories on developmental delays in craniosynostosis have also been described. The morphological changes that occur as a result of the premature fusion of the sutures, for instance, could have a secondary effect on the underlying brain. The progressive frontal bossing, which is so commonly seen in sagittal synostosis, could very well be the result of continued pressure on the growing frontal lobes, caused by the inability of the brain to expand in a lateral direction (Speltz, Kapp-Simon, Cunningham, Marsh & Dawson, 2004). Single-photon emission computed tomography studies of the frontal lobes in patients with trigonocephaly have shown diminished cerebral flow patterns. (Shimoji, Shimabukuro, Sugama & Ochiai, 2002). One could argue that this underdevelopment of the frontal lobe is due to premature closure of the metopic suture. Magnetic resonance imaging observations made by Aldridge et al. (2005) have indicated a degree of independence in the dysmorphology of the brain on the one hand and the skull on the other in cases of unicoronal craniosynostosis. Abnormalities in brain development have been shown to be persistent even after corrective surgery for sagittal synostosis. The findings of Shimoji et al. (2002) that even children with minimal morphological changes can present with severe neuropsychological impairments (such as autism and attention deficit/hyperactivity disorder) supports this theory. A primary brain malformation could even be the cause of the craniosynostosis. The role of the fibroblast growth factor receptor in the early development of both the brain and the skull makes a joint origin likely, because fibroblast growth factor receptor mutations can affect either one (Wilke, Gubbels, Schwartz & Richman, 1997).

Limitations of This Analysis

Because of the long-term retrospective design of our study, data for 43 patients were missing or incomplete, although statistical analysis revealed that these patients showed no significant

difference with regard to age, IQ, sex, diagnosis, or age at surgery. In the absence of a readily available control group, we used Davidoff's 2500 cases of normal skull radiographs described in 1936. In his paper he did not elaborate on the scientific methods used to obtain the BCP percentages.

Conclusions

The radiographic appearance of a BCP before the age of 18 months is an uncommon finding in healthy children. In our craniosynostosis study group, a 71.6% incidence of BCPs was seen up to this same age. The brain surface area covered by BCPs increased significantly in the first 3 years of age, which coincides with a period of rapid brain expansion. This increase is likely to be a sign of elevated ICP. Note, however, that the presence of a BCP did not have a significant long-term effect on intelligence levels. Its effect on more subtle developmental changes, such as reading and/ or spelling learning disabilities and behavioral disorders, may be more apparent. After the age of 3 years, the incidence of BCPs in craniosynostosis follows the same spreading pattern seen in the normal population.

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Drs. van der Meulen and van der Vlugt contributed equally to this work

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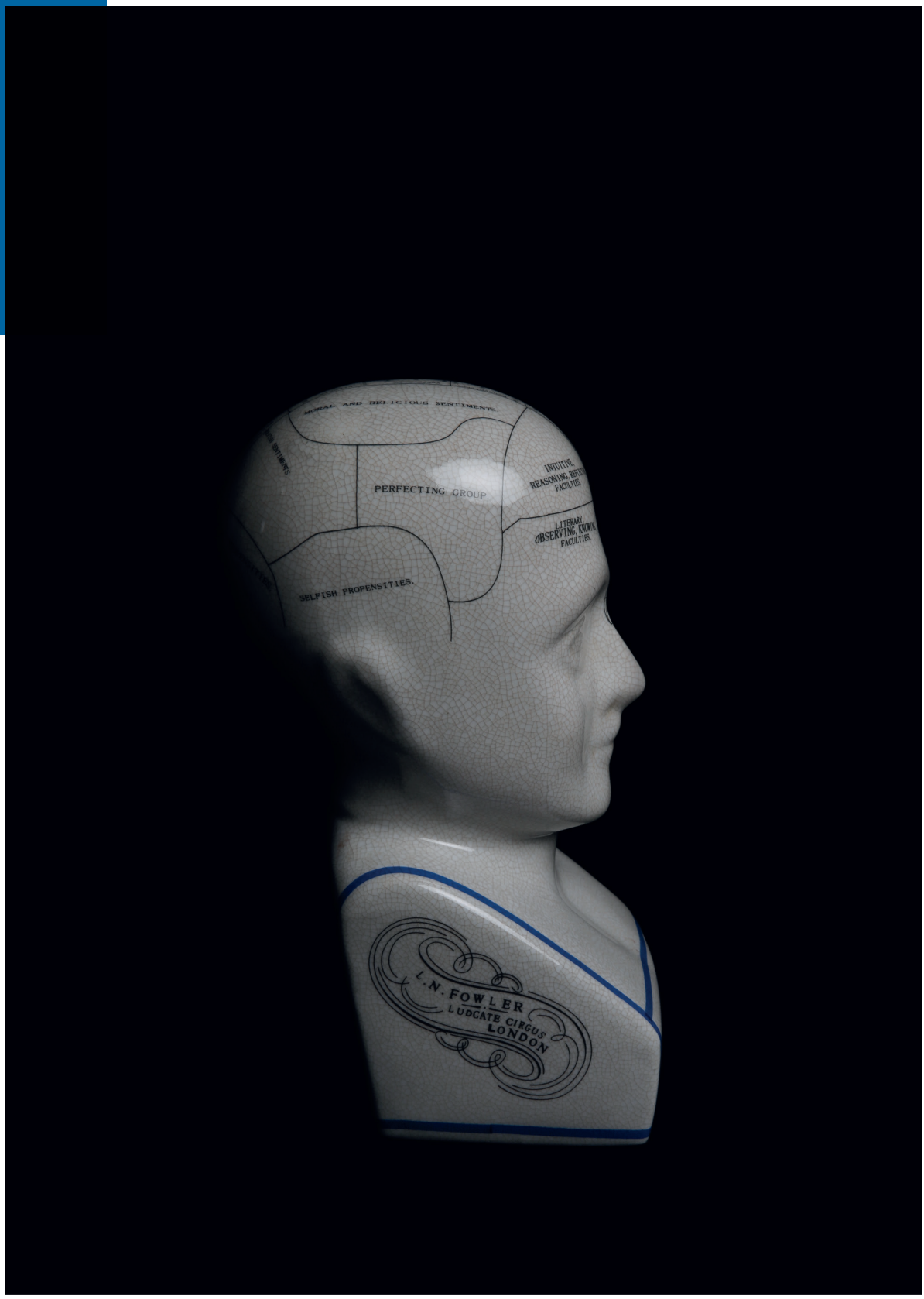
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CHAPTER 5

INSIGHT INTO THE PATHOPHYSIOLOGICAL MECHANISMS BEHIND COGNITIVE DYSFUNCTION IN TRIGONOCEPHALY

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ABSTRACT

Background: The relationship between trigonocephaly and cognitive problems might be explained by: secondary mechanical factors related to growth restriction of the skull, and primary structural defects caused by a shared mechanism related to brain developmental disorder(s) and skull malformation. However, because the exact pathophysiology remains unknown, we examined the pathophysiological mechanisms behind cognitive dysfunction in patients with trigonocephaly with an aim of providing a model for cognitive dysfunction based on routinely available variables.

Methods: Included were 72 operated patients with trigonocephaly who were operated on. Postoperatively, intelligence was assessed prospectively. The two independent variables, secondary mechanical and primary brain developmental mechanisms, were evaluated retrospectively. Computed tomographic imaging was used to assess skull volume and severity of the frontal stenosis (secondary mechanical factors), width of the central part of the lateral ventricles and other structural brain anomalies (primary brain developmental factors). Extracranial congenital anomalies were also taken into account.

Results: No association was found between secondary mechanical factors and postoperative IQ score. Width of the central part of the lateral ventricles and an interaction effect between this width and additional extracranial anomalies, showed a significant negative association with postoperative IQ.

Conclusion: Primary brain developmental disorders seem to play an important role in the development of cognitive problems in trigonocephaly. Assessment of the width of the central part of the lateral ventricle scores and additional extracranial congenital anomalies for the early prediction of cognitive problems in patients with trigonocephaly could be clinically valuable and can be performed using routinely available tools.

INTRODUCTION

Trigonocephaly is one of the most common forms of craniosynostosis (Kweldam, van der Vlugt, & van der Meulen, 2011; van der Meulen et al., 2009). The typically wedge-shaped skull, when viewed from above, originates from a premature stenosis of the metopic suture followed by a bilateral growth restriction of the forehead (Figure 1).

Children with trigonocephaly are thought to be at risk for cognitive problems, especially those with additional extracranial congenital anomalies (e.g. extra finger, ear or cardiac defects) (Bottero, Lajeunie, Arnaud, Marchac & Renier, 1998; Kelleher et al., 2006; Lajeunie, Le Merrer, Marchac & Renier, 1998; Shimoji, Shimabukuro, Sugama & Ochiai, 2002; van der Vlugt et al., 2012). In particular, trigonocephaly is associated with a high prevalence (9-13 percent) of intellectual disability compared to the prevalence reported in the general population (2.5 percent) (Lajeunie et al., 1998; Sidoti, Marsh, Marty-Grames & Noetzel, 1996; van der Vlugt et al., 2012). Trigonocephaly is also associated with structural brain anomalies, such as ventriculomegaly and agenesis of the corpus callosum (Aldridge, Marsh, Govier & Richtsmeier, 2002; Bottero et al., 1998), and with deformations of the brain that seem to mirror the wedge-shaped anterior vault, such as mediolateral expansion of the frontotemporal lobes (Aldridge et al., 2002). Notably, in these patients, the actual size or fluctuations in the size of the lateral ventricles are not associated with high intracranial pressure (Eide, 2003; Florisson et al., 2010).

To date, the pathophysiology behind the cognitive problems in trigonocephaly remains unknown; however, two hypotheses have been proposed (Speltz et al., 2007). The first implies that the metopic stenosis restricts skull growth, leading to increased mechanical pressure between the skull and its content (brain, blood and spinal fluid) (Arnaud, Renier & Marchac, 1995; Gewalli et al., 2001; Renier & Marchac, 1988; Renier, Sainte-Rose, Marchac & Hirsch, 1982) or to deformation of the underlying brain tissue (Aldridge et al., 2002). Some suggest that especially raised intracranial pressure, possibly resulting in hypoperfusion of the brain, is the major contributory factor behind the cognitive and behavior problems in these children (Arnaud et al., 1995; Gewalli et al., 2001; Renier & Marchac, 1988; Renier et al., 1982). Deformation of the frontal lobe could well be secondary to frontal stenosis and is theorized to cause distress in cortical connectivity, ultimately creating functional changes in the way the brain processes information (Speltz et al., 2007). Mathijssen et al. (1999) observed that the earlier the onset of metopic suture ossification, the more severe the frontal stenosis. However, reports on the relationship between cognitive functioning and mechanical mechanisms are difficult to interpret because of heterogeneous results. This might be attributed to methodological problems such as lack of information about patient

selection (Arnaud et al., 1995; Bottero, Lajeunie, Arnaud, Marchac & Renier, 1997; Gewalli et al., 2001; Mendonca et al., 2009; Renier & Marchac, 1988; Renier et al., 1982; Starr et al., 2010; Warschausky et al., 2005), the statistical approach (Bottero et al., 1997; Renier et al., 1982), small (sub)samples (Gewalli et al., 2001; Mendonca et al., 2009; Renier et al., 1982; Starr et al., 2010; Warschausky et al., 2005) and/or the use of non-validated instruments to assess cognitive functioning (Bottero et al., 1997).

The second hypothesis states that primary structural defects of the brain and skull might originate from a common cause (Kjaer, 1995). Only one study has analyzed associations between brain defects and cognitive functions in trigonocephaly (Bottero et al., 1997); unfortunately, the results are difficult to interpret due to the use of non-validated psychometric instruments and limited statistical power.

It is of clinical relevance to clarify the existence and extent of the effect of both mechanical factors and primary structural defects on cognitive functioning, because the current treatment of choice, (i.e. invasive cranioplastic surgery) focuses mainly on restoring volumetric dimensions. In addition, more knowledge on the early factors associated with cognitive problems might lead to a clinically valid model.

Therefore, this study aimed to test these hypotheses using well-validated instruments in a representative homogeneous sample of patients with trigonocephaly, and to assess both secondary (mechanical) and primary (congenital) factors leading to cognitive problems.

METHODS

Patient population

All patients with metopic synostosis who were surgically corrected by cranioplasty in the Erasmus Medical Center (Erasmus MC, Rotterdam) between May 1996 and August 2005 were approached for study enrollment postoperatively. Given that 70 percent of all fronto-orbital advancement procedures in the Netherlands are performed at Erasmus MC (Kweldam et al., 2011), this cohort is considered to be representative for the national situation.

Inclusion and exclusion criteria are described in Figure 2. All participants underwent preoperative three-dimensional computed tomographic scanning (mean age 7.0, SD 3.4 months), cranioplasty (mean age 11.0; SD 2.9 months) and cognitive assessment (mean age 6.0, SD 3.0 years). All were examined for the presence of extracranial congenital defects by a pediatrician or a clinical geneticist. Parental education level, assessed by interview, was based on the highest educational attainment of one of the parents/providers and was classified into two groups: above versus below the level of secondary school (secondary vocational education). Both parents of all patients gave written informed consent.

INDEPENDENT VARIABLES

Variables assessing growth restriction of the skull

Skull volume

Skull volume was calculated by a segmentation technique (Sgouros, Hockley, Goldin, Wake & Natarajan, 1999), allowing a composite computed tomographic image to be broken down into several simple objects that can be easily manipulated and reconstructed in three dimensions. Image-J software (Rasband, 1997) was used to calculate individual slice volumes by multiplying the surface of the outline by the slice thickness. All slice volumes added together resulted in the total volume of the intracranial cavity. The volumetric skull measurements were validated by comparison with real-time volumetric measurements of five human skulls (the property of our anatomical department) [intraclass correlation coefficient (of 0.96]. In two patients computed tomographic scan data were incomplete, leaving 70 patients for data analysis. Following Sgourgous (Sgouros, 2005), who suggested that especially patients with single suture craniosynostosis aged 6 months or younger were at risk for smaller skull volumes, a separate analysis was made including only patients aged 6 months or younger.

Frontal stenosis

The severity of frontal stenosis was calculated by measuring the ratio of the interparietal distance, between the outer skull tables at the widest points of the skull, to the intercoronal distance, between the outer skull tables at the level of the anterolateral corners of the lateral ventricles (Figure 3). This method was introduced by Posnick et al. in 1994 and further modified by Bottero et al. (1998). The inter-observer and the intra-observer reliability for our measurements are high (intraclass correlation coefficients of 0.91 and 0.99, respectively).

Variables assessing primary brain developmental factors

Ventricle width

Widened ventricles in children with trigonocephaly are not associated with hydrocephaly (Eide, 2003; Florisson et al., 2010), which justifies measurement of the ventricles. Because no validated methods are available to measure the lateral ventricular width we developed our own method, (i.e. the width of the central part of the lateral ventricles). Notably, this method is not strongly dependent on sagittal angulation and therefore counteracts possible data loss, as a large proportion of our patients (n=25) had older computed tomographic scans with a relatively large slice thickness.

The width of the central part of the lateral ventricles is assessed by measuring the ratio of the maximum width of the central part of the lateral ventricles by the maximum width of the skull, as shown in Figure 4. Outcomes result in a score of 0-1. Although the width of the central part of the lateral ventricles was not developed to assess hydrocephalus, it does correlate well (intraclass correlation coefficient of 0.74) with the fronto-occipital horn width ratio (developed for hydrocephalus) (Jamous, Sood, Kumar & Ham, 2003). Moreover, the width of the central part of the lateral ventricles is easy to measure and our measurements showed a very high inter-rater and intra-observer reliability (intraclass correlation coefficient of 0.96 and 0.91, respectively).

Other brain anomalies

In all 72 patients, computed tomographic scans were examined thoroughly by a senior pediatric neuroradiologist, for the presence of brain abnormalities other than ventriculomegaly.

Dependent variable

Intelligence Quotient (IQ)

Trained psychologists performed cognitive assessments for all patients. Mean age at assessment was 6.0 (SD 3.0) years.

Intelligence level was determined using one of three intelligence tests: 1) In 21 patients aged 2-3 (mean 2.5; SD 0.4) years, the IQ score was assessed using the Dutch version (Mullen, 1995) of the Mullen Scales of Early Learning (Kort et al., 2005; Stinissen, Willems, Coetsier & Hulsman, 1970); 2) for children aged 4-6 years (n=27) the IQ score was estimated with a four-subtest short form of the Dutch Versions (Hendriksen J, 1997; Kort et al., 2005; Stinissen et al., 1970) of the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 2002); and 3) for children aged 7-16 years (n=24) the Wechsler Intelligence Scale for Children was used (Wechsler, 1991, 1997). Subtest scores were converted to a composite score that was used to estimate the IQ score, which correlates highly with the Full-scale IQ (Kaufman, Kaufman, & Mclean, 1994; Thompson, 1995; Tsushima, 1994). Additional congenital extracranial anomalies and parental education were considered possible confounders of the relationship between the independent variables and IQ scores. Age and sex were included in all analyses, as these are often direct or proximal factors in cognitive research.

STATISTICAL ANALYSIS

Pearson's correlation coefficients were used to identify associations between the IQ score and the various pathophysiological factors and covariates. Next, general linear models were used to assess the effect of each mechanical and primary brain developmental variable on the IQ score, controlling for additional extracranial congenital anomalies, sex, age, and parental educational level. Possible first-order interaction effects were evaluated for all main predictors. Model selection was based on (adjusted) R-squared and model assumptions were checked graphically. Sensitivity analyses were planned to assess the effects of extreme values and incomplete data. The level of statistical significance was set at $p<0.05$.
The SPSS, version 20 for Windows, was used for all analyses.

RESULTS

Patient characteristics
Of the 72 patients, 20 (28 percent) were affected by additional extracranial congenital anomalies; 15 (75 percent) had one extracranial anomaly and 5 (25 percent) showed anomalies in two different organ systems. Anomalies of the upper limb were the most common (Table 1). Table 2 presents the demographic and clinical characteristics of the study population. The IQ scores of individual patients with extracranial congenital anomalies are shown in Table 3. The mean IQ levels of the subgroups of patients with extracranial congenital anomalies showed no significant differences between each other. The IQ scores showed no significant difference between or within the IQ assessment tools used (analysis of variance, $F=0.02$ $p=0.98$). Except for widened lateral ventricles, no other structural brain anomalies were detected.

Table 1. Frequencies and percentages of congenital extracranial anomalies of all patients with trigonocephaly (n=72). Subdivision based on the study of Bottero et al. (Bottero et al., 1998).

Extracranial anomaly	n	%
Upper limb anomalies	10	40
- simian crease (n=6)		
- hypoplasia digitus I (n=1)		
- clinodactyly digitus V (n=1)		
- camptodactyly digitus V (n=1)		
- symbrachydactyly (n=1)		
Lower limb anomalies	3	12
- enlarged hallux (n=1)		
- infraductus digitus IV (n=1)		
- superductus digitus II (n=1)		
Cardiac anomalies	6	24
- atrial septal defect type II (n=3)		
- ventricular septal defect (n=3)		
Facial anomalies	5	20
- dysplastic ears (n=3)		
- cleft palate and micrognathia (n=1)		
- cleft lip/alveolus and palate (n=1)		
Hearing impairment	1	4
- enlarged vestibular aquaduct (n=1)		
Total	25	100

Table 2. Demographic and clinical characteristics of the patients.

	Prevalence/mean	*Range (SD)*	*n*
Gender (male)	83%		*72*
Age at cognitive assessment (in years)	5.9	1.4-12.4 (3.0)	*72*
High education level (parents)	49%		*71*
Extracranial congenital defects	28%		72
Mechanical factors			
- Skull volume (ml)	920.6	490-1258 (163)	70
- Frontal stenosis #	1.24	1.03-1.38 (0.07)	71
Brain anomalies			
- Width lateral ventricles (WCLV ratio)	0.18	0.08-0.35 (0.05)	69
- Structural anomalies	0		72
Cognitive functioning			
- IQ points*	101.0	52-147 (20.3)	72

Ratio of the interparietal distance to the intercoronal distance; * 8% intellectually disabled (IQ <70)

Table 3 IQ scores of individually numbered patients with extracranial congenital abnormalities.

	IQ score
Upper limb	
(1) Simian crease dexter	92
(2) Simian crease dexter	98
(3) Simian crease both sides, infraductus digitus IV both sides	99
(4) Simian crease both sides, superductus digitus II both sides	90
(5) Simian crease sinister, dysplastic ears	106
(6) Simian crease both sides, dysplastic ears	79
(7) Hypoplasia digitus I, ventricular septum defect	92
(8) Clinodactyly digitus V both sides	56
(9) Camptodactyly digitus V	123
(10) Symbrachydactyly	83
Mean IQ level (95% confidence interval)	92 (*80 – 104*)
Lower limb	
(11) Enlarged hallux both sides	114
(3) Infraductus digitus IV, simian crease both sides	99
(4) Superductus digitus II both sides, simian crease both sides	90
Mean IQ level (*95% confidence interval*)	101 (*86 – 116*)
Cardiac anomalies	
(12) Atrial septal defect type II	102
(13) Atrial septal defect type II	112
(14) Ventricular septum defect	63
(15) Ventricular septum defect (small)	114
(16) Atrium septum defect type II	100
(7) Ventricular septum defect, hypoplasia digitus I	92
Mean IQ level (95% confidence interval)	97 (*81 – 113*)
Facial anomalies	
(17) Dysplastic ears	110
(5) Dysplastic ears, simian crease sinister	106
(6) Dysplastic ears, simian crease both sides	79
(18) Cleft palate and micrognathia	54
(19) Cleft lip/alveolus and palate	52
Mean IQ level (95% confidence interval)	80 (*54 – 106*)
Hearing impairment	
(20) Enlarged vestibular aquaduct with functional hearing loss dexter	94

Effects on IQ scores

Table 4 presents the regression coefficients for the effects of preoperative factors on the postoperative IQ score; no association was found between the IQ score and mechanical factors (skull volume, or frontal stenosis). The skull volume of patients aged 6 months or younger also showed no significant association with IQ scores. As shown in Figure 5, width of the central part of the lateral ventricles and an interaction effect between width of the central part of the lateral ventricles and extracranial anomalies, showed a significant negative association with postoperative IQ. This model suggests that, for patients with a 5 percent ventricular width above average and extracranial anomalies, a lower mean IQ score

of approximately 25 points (-9.75 + -0.37*5 + -2.58*5 = 24.5) (Table 4) can be expected (all other variables remained constant). Sensitivity analyses showed that this combined effect on the IQ score was limited to a more extreme ventricular width, in combination with additional extracranial congenital anomalies. The model including the interaction effect of width of the central part of the lateral ventricles with extracranial anomalies extracted 19 percent of the variance of postoperative IQ score (adjusted R^2=0.19; p<0.05).

Table 4. Multiple linear regression models for postoperative IQ score with different regressors: preoperative mechanical factors (skull volume and frontal stenosis) or preoperative primary brain developmental factor (ventricular width), after controlling for extracranial anomalies and demographic characteristics.

	Mechanical		**Primary brain developmental**
	Skull volume Estimate (SE)	**Frontal stenosis Estimate (SE)**	**Ventricular width % Estimate (SE)**
Preoperative factor	0.005 (0.02)	-31.7 (37.99)	-0.36 (0.67)
Extracranial anomalies (yes/no)	-13.4 (5.72)**	-13.8 (5.68)*	-10.0 (5.35)*
Preoperative factor: Extracranial anomalies	-	-	-2.57 (1.07)**
Gender (male)	5.25 (6.78)	4.27 (6.85)	6.98 (6.25)
Age at cognitive assessment#	-0.33 (1.07)	-0.13 (0.76)	-0.42 (0.74)
Parents education (high)	7.08 (5.07)	7.37 (4.98)	8.35 (4.63)*
Adjusted R-squared	0.04	0.05	0.19
F-statistic (DF)	1.482 (5-61)	1.626 (5-61)	3.489 (6-60)
p-value	0.209	0.166	0.005

years mean centered; * p < 0.10, ** p < 0.05

DISCUSSION

The aim of this study was to gain more insight into the pathophysiological mechanisms behind cognitive dysfunction in patients with trigonocephaly, and provide a model for cognitive dysfunction based on independent and routinely available variables. A significant negative association was found between ventricular width and IQ score, particularly in patients with additional extracranial congenital anomalies. More specifically, according to our model, a lower mean IQ of 25 points is to be expected in patients with extracranial congenital anomalies when the width of the central part of the lateral ventricles is 5 percent above average. A preoperative assessment of both the width of the central part of the lateral ventricles scores and additional extracranial congenital anomalies could therefore be of clinical value in predicting possible cognitive problems in patients with trigonocephaly. Factors secondary to growth restriction of the skull were not significantly associated with the

postoperative IQ score. This may support the hypothesis that primary brain developmental disorders affect the development of cognitive problems in trigonocephaly.

Although we present one of the largest study samples of patients with trigonocephaly, the absolute number of participants was relatively small. In particular, some subgroup analyses might suffer from low statistical power due to the small numbers. Moreover, there may be additional mechanisms that affect the cognitive function of children with trigonocephaly besides those described in the literature. All patients in the present study had undergone, for example, fronto-supraorbital remodeling and advancement surgery. As a consequence, possible positive or negative effects of the surgery on cognitive functioning at a later age cannot be evaluated in this study population. However, introducing a control group of children not undergoing surgery is not feasible, given the major ethical issues involved.

Mechanical forces between the skull and its content as predictor for cognitive problems

The domino effect of diminished skull growth leading to a smaller intracranial volume resulting in increased intracranial pressure is still thought to be the accumulation of events leading to cognitive impairment in patients with craniosynostosis. This 'mechanical' hypothesis is mostly based on older studies (Arnaud et al., 1995; Renier & Marchac, 1988; Renier et al., 1982), which were hampered by small heterogeneous study populations and insufficient statistical analyses. However, to date, this hypothesis remains the main argument for cranial vault surgery (Garza & Khosla, 2012). In the Netherlands, treatment guidelines advise corrective cranioplasty before age 1 year for patients diagnosed with trigonocephaly. However, the present results show no significant association between the factors secondary to growth restriction of the skull and cognitive functioning.

Following the first step of the hypothesized mechanical cascade, diminished skull growth in craniosynostosis will lead to a smaller intracranial volume. Indeed, Sgourous observed that skull volumes of children with single-suture craniosynostosis, including trigonocephaly, aged 6 months or younger, were smaller in comparison to healthy controls (Sgouros, 2005).

In the present study, the variance in preoperative skull volume showed no significant association with IQ scores, not even in the subgroup of patients aged 6 months or younger. Furthermore, it was recently reported that, after 1 year, without cranial vault surgery the intracranial volume of children with single-suture craniosynostosis (including trigonocephaly) is equal to that of healthy controls (Maltese et al., 2014; Sgouros, 2005). Thus, it appears that, in these latter patients, the compensatory growth mechanisms of the skull (also without surgery) were sufficient to prevent interference with cognitive development because of growth restriction of the skull. Our results, combined with the above-mentioned findings (Maltese et al., 2014; Sgouros, 2005), do not support the mechanical hypothesis proposing

that diminished skull growth is the cause of neurodevelopmental problems in children with trigonocephaly.

An alternative mechanical pathway implies that deformation of the frontal lobe causes distress in cortical connectivity, ultimately creating functional changes in the way the brain processes information (Aldridge et al., 2002; Speltz et al., 2007). This hypothesis is supported by Malthese et al. (2014) who showed that the intracranial volume anterior to the coronal sutures is 30 percent less in patients with trigonocephaly compared to healthy controls. Notably, in single-suture craniosynostosis, computed tomographic scans are routinely performed and, therefore, skull deformation is often used as an indirect measure for brain deformation. The first to investigate associations between frontal skull deformation and cognitive problems was Kapp-Simon (1994); however, outcomes of her self-made four-point cumulative grading system for the severity of the deformity were not significantly related to developmental scores in 45 single-suture craniosynostosis patients. In contrast, Bottero et al. (1998), using the same method as our group to measure frontal stenosis, suggested that severe frontal stenosis was a strong predictor for cognitive and behavioral problems at a mean age of 6 years in a homogeneous sample of trigonocephaly patients. However, it is likely that the use of non-validated parental interviews biased their outcome and resulted in overrated negative parental judgment of (especially) patients with severe frontal stenosis. Three later studies (Mendonca et al., 2009; Starr et al., 2010; Warschausky et al., 2005) were unable to demonstrate an association between frontal stenosis, and cognitive and behavioral function in patients with trigonocephaly. In these studies, however, cognitive functioning was assessed before the age of 3 years, which is reported to correlate poorly with later cognitive functioning (Roze et al., 2010). The present study included a substantial proportion of patients older than 4 years (51/72), so that long-term cognitive functioning could be assessed. Our results show that the IQ score was not affected by the severity of the frontal stenosis, not even at a later age. The findings of the present study combined with the above-mentioned findings in literature (Mendonca et al., 2009; Starr et al., 2010; Warschausky et al., 2005) do not support the mechanical hypothesis proposing that frontal skull deformation is the cause of neurodevelopmental problems in children with trigonocephaly.

Congenital brain defects as predictor for cognitive problems

The second hypothesis explains both the cognitive deficits and abnormal skull shape through a shared primary developmental pathophysiological mechanism (Kjaer, 1995; Raybaud & Di Rocco, 2007; Speltz, Kapp-Simon, Cunningham Marsh & Dawson, 2004). With the introduction of the computed tomographic scan, the association between metopic synostosis and brain anomalies became apparent. Although ventriculomegaly and corpus callosum anomalies

are the most commonly reported findings (Aldridge et al., 2005; Bottero et al., 1998; Cinalli et al., 1998), in our study widened lateral ventricles were the only brain anomaly observed.

The actual size or fluctuations in size of the lateral ventricles in patients with single-suture craniosynostosis is not associated with the level of increased intracranial pressure or the presence of papilledema in patients with craniosynostosis (Eide, 2003; Florisson et al., 2010). Moreover, Collmann et al. (2005) indicated that widened ventricles in children with single-suture craniosynostosis, especially trigonocephaly, are likely to be linked to coincidental cerebral maldevelopment or secondary to involution of brain parenchyma. Furthermore, from an embryological point of view, ventriculomegaly can be explained by the transformation of somewhat balloon-shaped into C-shaped lateral ventricles during the outgrowth of the developing cerebral hemispheres. During this period, the hemispheres expand in all directions (Moore, 2013), also growing out into the cavities of the balloon-shaped ventricles, resulting in a relative decrease in ventricular width (Nieuwenhuis, 2008). As a consequence, insufficient outgrowth into the cavities will lead to ventriculomegaly. Because ventriculomegaly is not associated with intracranial pressure (Eide, 2003; Florisson et al., 2010) we believe that the size of the ventricles in patients with trigonocephaly is likely to reflect the degree of insufficient outgrowth, which is indirectly linked to a primary brain developmental problem.

Bottero et al. (1998) were the first to suggest that ventriculomegaly (erroneously indicated as hydrocephalus) was associated with low IQ in their cohort of 76 patients with metopic synostosis. In our population we narrowed this observation to patients with additional extracranial congenital anomalies, since the observed increased lateral ventricular width had the highest negative impact in this subset of patients. This result supports the observation that children presenting with extracranial congenital anomalies (but without trigonocephaly) are reported to be overrepresented in neurodevelopmental disorders such as schizophrenia, autism, hyperactivity, epilepsy, and intellectual disability (Ismail, Cantor-Graae & McNeil, 2000; Trixler, Tenyi, Csabi, Szabo & Mehes, 1997). Our observation that ventricular width, particularly in patients with additional extracranial congenital anomalies, was associated with cognitive problems is an additional argument that supports the hypothesis that primary brain developmental disorders affect the development of cognitive problems in trigonocephaly.

In general, the extracranial anomalies observed in our study have an embryological basis regulated by the common toolbox of developmental genes resulting in comparable biological mechanisms and developmental principles, related to different time frames and different locations in the body (Luijsterburg, Rozendaal & Vermeij-Keers, 2014). Unfortunately, our subgroup of children with extracranial anomalies was too small to reveal a statistical difference. Nevertheless, it is tempting to consider a relationship between the low (but not

significantly different) IQ score in patients with facial anomalies and the fact that brain and facial development are closely related to each other in utero, because the neural crest (Ten Donkelaar, 2014), face and brain originate from the same (neuro)ectodermal layer (O'Rahilly & Muller, 1989). Therefore, it seems feasible that that facial anomalies in combination with intracranial anomalies could coincide with an aberrant neurodevelopment (Cheung et al., 2011).

Imaging studies in healthy children show that cognitive function correlates with white matter architecture of different regions in the brain (Nagy, Westerberg & Klingberg, 2004; Schmithorst, Wilke, Dardzinski & Holland, 2005), and imaging studies in craniosynostosis patients show that white matter integrity was altered compared to healthy controls (Beckett et al., 2014; Florisson et al., 2011). Raybaud and Di Rocco (2007) hypothesized that the relationship between craniosynostosis and white matter defects might be caused by the lack of interaction with L1 cell adhesion molecules and the fibroblast growth factor receptor. Notably, non-progressive ventriculomegaly, or insufficient outgrowth into the cavities of the ventricles, can also be explained by a diffuse lack of white matter, which is associated with cognitive problems (Leviton & Gilles, 1996; Raybaud & Di Rocco, 2007). It is tempting to suggest that a diffuse lack of white matter, reflected by widened lateral ventricles, plays a role in the cognitive disfunctioning of patients with trigonocephaly.

CONCLUSIONS

Our findings tend to support the hypothesis that primary brain developmental disorders affect the development of cognitive problems in trigonocephaly. Assessment of width of the central part of the lateral ventricles scores and additional extracranial congenital anomalies for the early prediction of cognitive problems in patients with trigonocephaly could be valuable and can be performed preoperatively using routinely available tools. Additional studies combining neuropsychology, genetics and latest imaging methods are needed to further elucidate the complex pathophysiological process behind the association between cognitive dysfunction and trigonocephaly.

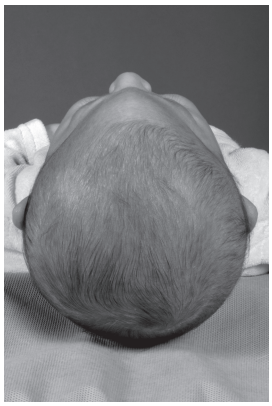

Figure 1. Photograph showing a 9-month-old boy with trigonocephaly.

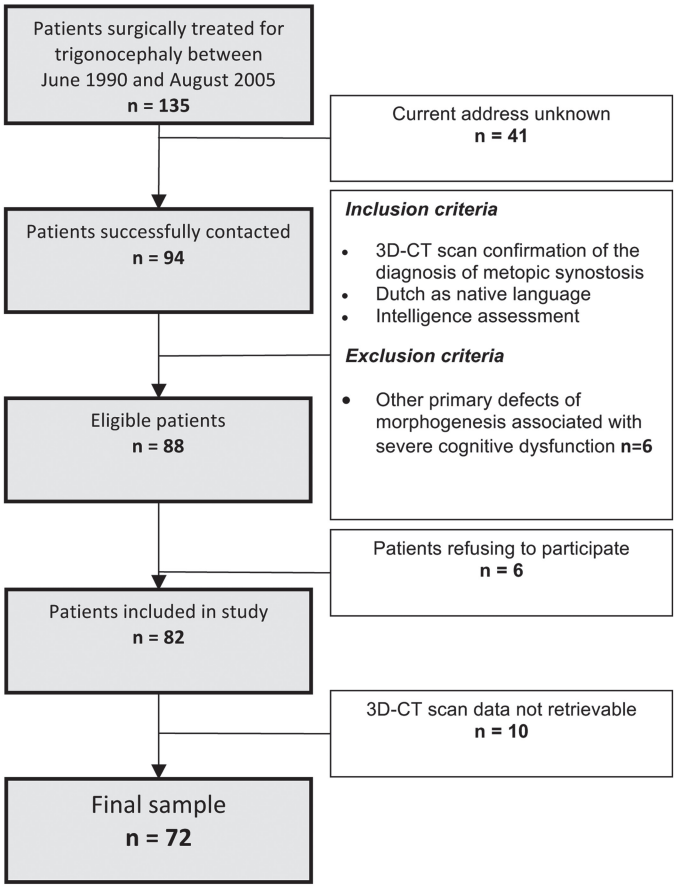

Figure 2. Flowchart showing the selection of patients for his study.

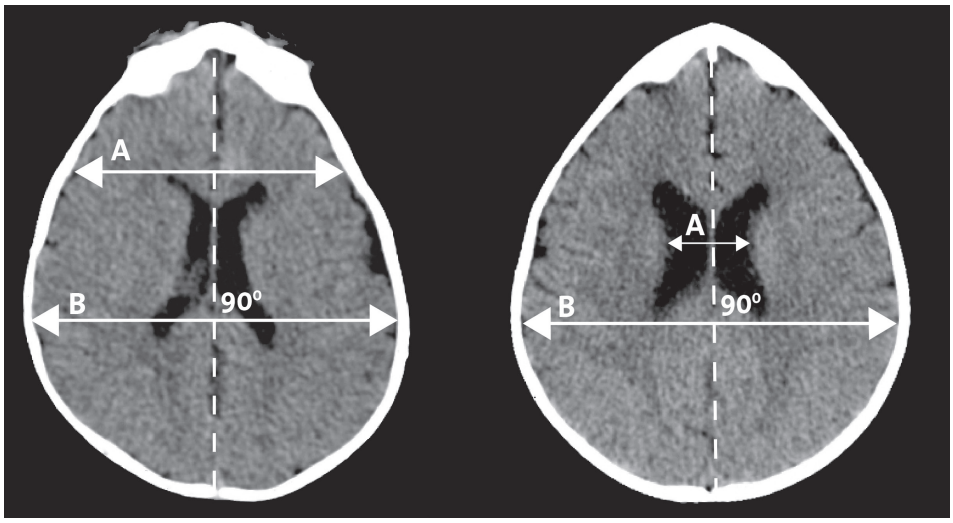

Figure 3. CT-scan showing the severity of frontal stenosis measuring the ratio of the interparietal distance (B) to the intercoronal distance (A) (3, 26).

Figure 4. CT-scan showing the width of the central part of the lateral ventricles (width of the central part of the lateral ventricles) assessed by the ratio of the maximum width of the central part of the lateral ventricles (A) by the maximum width of the skull (B).

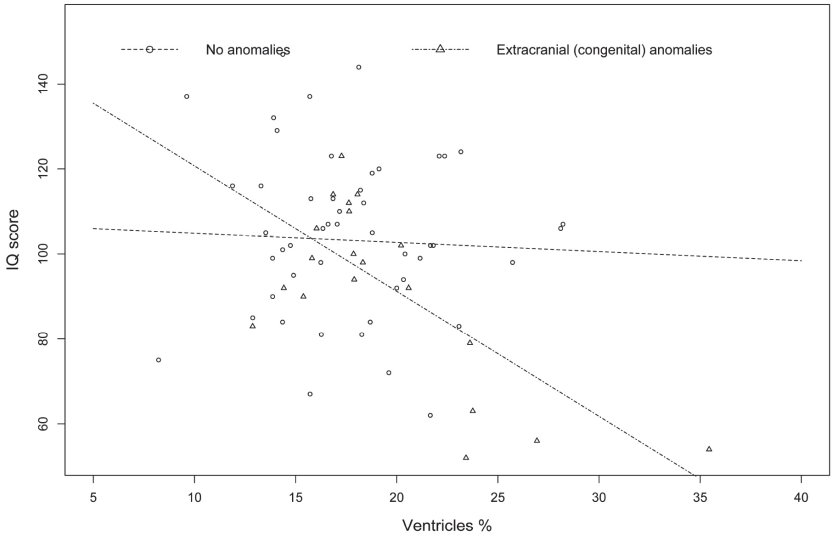

Figure 5. Scatter plot of the association between IQ and width of the central part of the lateral ventricles including the interaction effect with extracranial anomalies.

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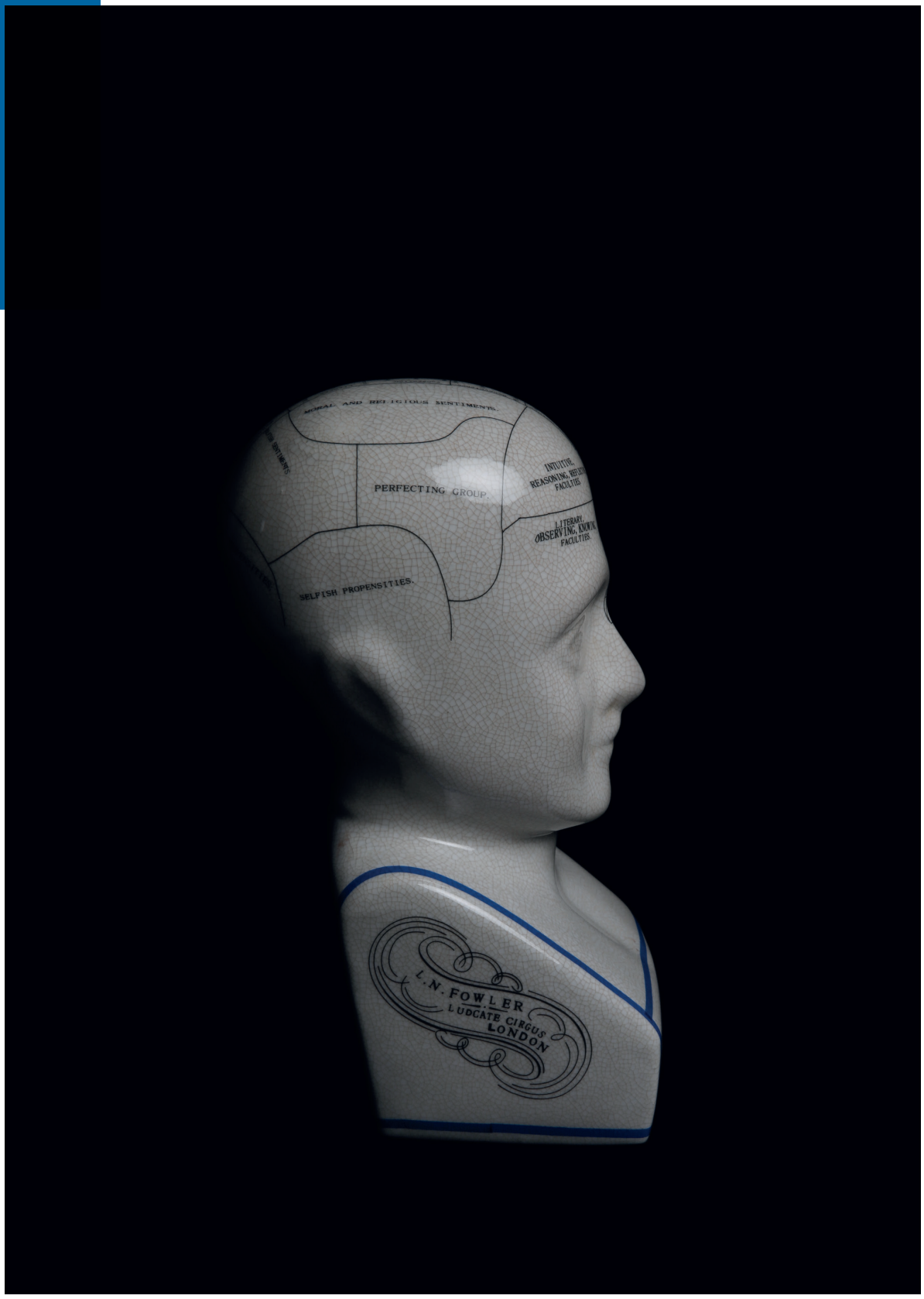
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CHAPTER 6

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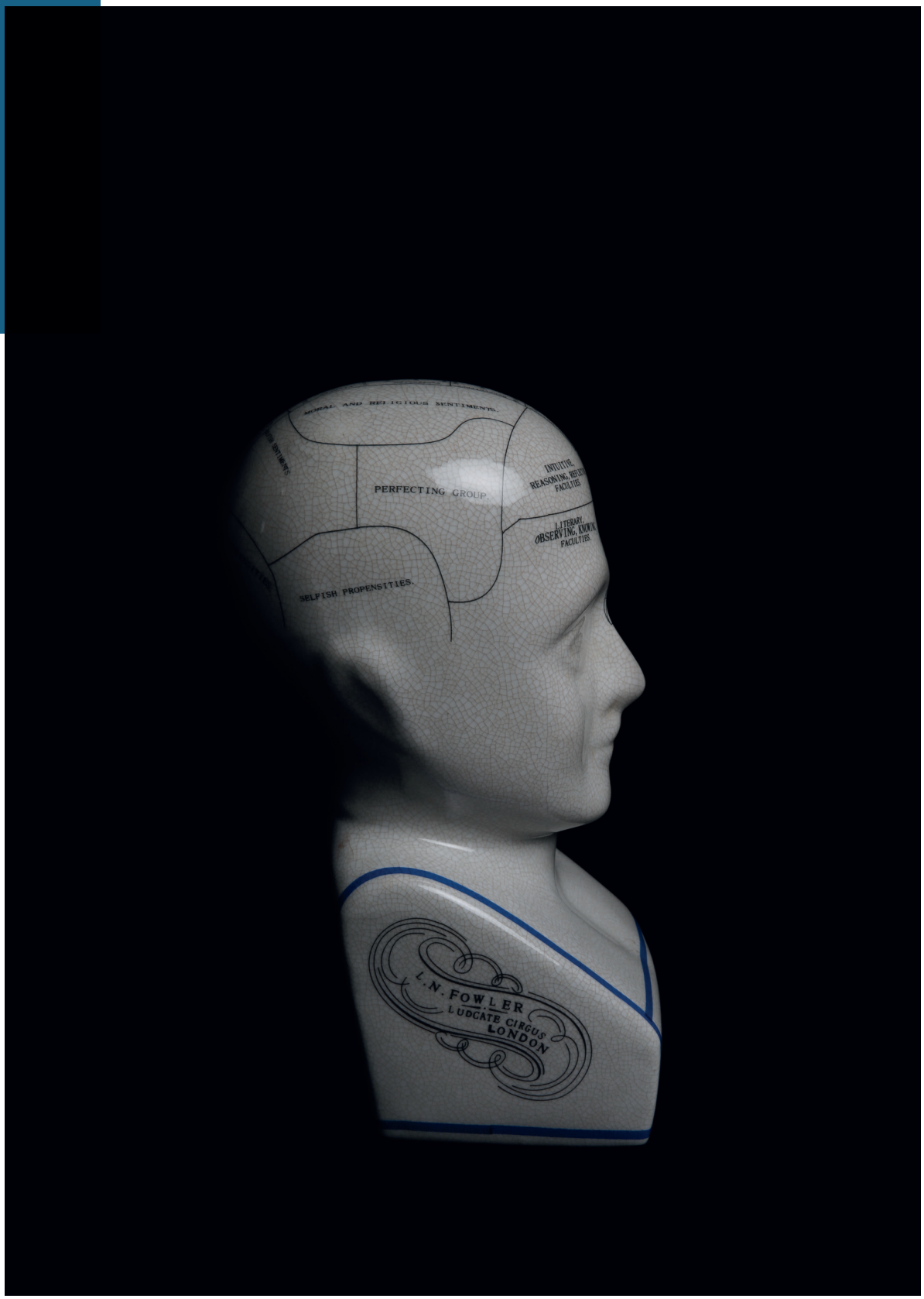
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CHAPTER 7

GENERAL DISCUSSION AND CONCLUSION

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GENERAL DISCUSSION AND CONCLUSION

Craniosynostosis has long been associated with cognitive impairment, as well as with behavioral and emotional problems. However, methodological limitations, including small sample sizes and the use of non-validated instruments, limit the robustness of the findings of most earlier studies. Consequently, the association between craniosynostosis and cognitive and behavioral functioning, as well as potential mechanisms underlying this association, remain unclear.

The work presented in this thesis aimed to gain more insight into the prevalence of (neuro)cognitive, behavioral and emotional problems in children with craniosynostosis (**Part 1**) and to extend knowledge on the possible etiology of cognitive problems in children with craniosynostosis (**Part 2**).

This chapter discusses the main results of our research. In addition, the strengths and limitations of the studies are addressed, and recommendations are made for future research and practice.

MAIN FINDINGS

Part 1

- In craniosynostotic patients with IQ scores *less* than 85, the prevalence of behavioral and emotional problems was significantly higher than in the normative population.

- In craniosynostotic patients with IQ scores *above* 85, there was no significant difference in the prevalence of behavioral and emotional problems compared with that in the normative population

- No significant difference in the prevalence of behavioral and emotional problems was found between single-suture synostosis (SSC) and complex craniosynostosis (CC).

- IQ score was strongly associated with behavioral and emotional problems in children with craniosynostosis, as is also the case in children *without* craniosynostosis.

- On group level, 38 percent of children with trigonocephaly had either autistic features and/or an IQ score less than 85 and/or met the criteria for attention deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder

- In patients with trigonocephaly, there was no significant difference in the prevalence of features of autism spectrum disorders, attention deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder, compared with that in community/ school samples.

- A significantly higher prevalence of intellectual disability (9 percent) was found in patients with trigonocephaly compared with the 2.5 percent expected to be found (according to normal distribution) in the general population.

Part 2

*Association between intracranial pressure and cognitive functioning (**first hypothesis**):*

- Presurgical radiographs showed no significant correlation between IQ scores and behavioral and emotional problems, and the 'copper-beaten' appearance of the skull.

- The skull volume of patients with trigonocephaly aged 6 months or younger showed no significant association with IQ scores later in life.

*Association between skull deformation and cognitive functioning (**second hypothesis**):*

- Preoperative severity of the frontal stenosis in patients with trigonocephaly was not associated with IQ score later in life.

*Association between primary brain deformation and cognitive functioning (**third hypothesis**):*

- In children with trigonocephaly, width of the central part of the lateral ventricles, as well as an interaction effect between width of the central part of the lateral ventricles and extracranial anomalies, showed a significant negative association with IQ score later in life.

*Association between open surgical treatment and cognitive problems (**fourth hypothesis**):*

- Duration of surgery was significantly negatively associated with IQ score later in life.

- When duration of surgery was taken into account, cumulative exposure to anesthetics showed no significant added effect on IQ score later in life.

Part I – Prevalence of cognitive and behavioral and emotional problems in craniosynostosis: integration of results

In this section of the thesis, the aims were to assess the prevalence of behavioral and emotional problems in craniosynostosis, taking into account the potential moderating role of the IQ score. We found that children with craniosynostosis and IQ scores *above* 85 did not have a higher prevalence of behavioral and emotional problems compared to children in the norm group. This finding was replicated in a subgroup of patients with trigonocephaly alone.

Nevertheless, when IQ scores in craniosynostosis patients were *below* 85, the prevalence of deviant scores on the Child Behavior Checklist in the domains Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Internalizing and Total Problems, were significantly higher than in the normative population. Moreover, in the sample with mainly children with trigonocephaly with IQ scores under 85, we found that 7 of 10 patients either

had autistic features and/or met the DSM-IV criteria for attention deficit disorder, oppositional deficit disorder, or conduct disorder. Moreover, on a group level, 38 percent of children with trigonocephaly had either autistic features, and/or an IQ score less than 85, and/or met the criteria for attention deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder. These latter findings were in line with most earlier reports on natural groups of children with trigonocephaly, reporting a prevalence of 31-37% for behavioral and emotional problems (Bottero, Lajeunie, Arnaud, Marchac & Renier, 1998; Kelleher et al., 2006; Sidoti, Marsh, Marty-Grames & Noetzel, 1996).

The studies in this thesis show that, in children with craniosynostosis, IQ scores were highly associated with behavioral and emotional problems. Nevertheless, high rates of behavioral and emotional problems are also observed in populations with low intelligence levels without craniosynostosis (Dekker, Koot, van der Ende & Verhulst, 2002). Therefore, based on the present findings, we suggest that the IQ score, rather than (the complexity of) craniosynostosis, explains the increased prevalence of behavioral and emotional problems in children with craniosynostosis, as was also reported in earlier studies.

Furthermore, in our sample of children with trigonocephaly alone, we found a 9% prevalence of intellectual disability compared to the expected 2.5% based on the normal distribution. This outcome is in line with other studies that reported a high prevalence of intellectual disability (10-13%) (Lajeunie, Le Merrer, Marchac & Renier, 1998; Sidoti et al., 1996). Notably, whilst performing the studies in this thesis, Speltz et al. were able to include 182 cases of SSC and showed that patients with trigonocephaly, as well as unicoronal and lambdoid synostosis, had lower intelligence levels than the most common form of craniosynostosis, i.e. sagittal synostosis (Speltz et al., 2015). Therefore, children with trigonocephaly seem to be at higher risk to develop intellectual disability, and have lower mean IQ scores than the most common form of SSC, i.e. scaphocephaly.

Part II – Potential pathophysiological pathways behind neurocognitive problems in patients with craniosynostosis

In this part of the thesis the aim was to extend the existing knowledge by examining four potential pathways related to the etiology of cognitive problems in children with craniosynostosis.

*Neurocognitive problems due to high intracranial pressure (**first hypothesis**)*

The first hypothesis implies that the craniosynostosis restricts skull growth, which leads to increased mechanical pressure between the skull and its content (brain, blood, and spinal fluid) (Arnaud, Renier & Marchac, 1995; Gewalli et al., 2001; Inagaki et al., 2007; Shimoji

& Tomiyama, 2004; Siddiqi et al., 1995). We investigated whether the presence of skull beaten-copper patterns (BCP) before age 18 months (Davidoff, 1936), as indirect marker of high intracranial pressure (ICP) (Tuite et al., 1996), might be associated with cognitive or behavioral problems in children with craniosynostosis. Remarkably, neither the quantity, age at presentation or location of BCP were associated with either cognitive or behavioral functioning later in life. Meanwhile, our findings on BCP could be interpreted as an indication of an increase of mechanical forces between the skull and its contents: i.e. we observed that the percentage of skull area occupied by BCP was greater in patients with CC (32.2%) compared to patients with SSC (12.8%). Meanwhile, other studies have shown that CC is associated with higher ICP compared to SSC (Tamburrini, Caldarelli, Massimi, Santini & Di Rocco, 2005).

Secondly, although Davidoff reported that BCP before age 18 months was a rare finding (Davidoff, 1936), in craniosynostosis we observed a 73% prevalence of BCP before age 18 months. Thirdly, the spreading pattern of BCP seemed to coincide with the pattern of brain growth. During the rapid volume expansion of the normal developing brain in the first three years of life (Courchesne et al., 2000), a highly significant yearly *increase* of BCP was found in our study group; this was followed by a significant yearly *decrease* when normal brain growth declined. Accordingly, although the three findings related to BCP in craniosynostosis indirectly suggested an increase of mechanical pressure between the skull and its content in patients with SSC, our studies found no association between BCP and cognitive, behavioral and/or emotional functioning later in life.

The second indirect marker investigated in this thesis was preoperative skull volume. Moreover, according to Sgouros et al., (2005) in children with craniosynostosis skull growth is diminished in the first 6 months of life. Nevertheless, after one year, without cranial vault surgery, the intracranial volume of children with SSC (including trigonocephaly) is equal to that of healthy controls (Maltese et al., 2014; Sgouros, 2005). This led us to investigate whether skull growth before age 6 months interfered with cognitive functioning later in life. Results of our studies on the second indirect marker showed that preoperative skull volume in patients with trigonocephaly aged ⩽ 6 months, had no direct association with IQ score. Therefore, although skull growth is diminished in the first 6 months of life in patients with craniosynostosis, our study did not show a significant association between skull volume and cognitive functioning.

The finding that neither skull volume nor BCP are associated with IQ score, argues against the long-existing hypothesis that increased ICP in SSC causes neurodevelopmental damage of cerebral tissue by compromising neuronal oxygenation (Renier & Marchac, 1988). However, this latter 'mechanical' hypothesis is mostly based on older studies (Arnaud et al.,

1995; Gewalli et al., 2001; Inagaki et al., 2007; Shimoji & Tomiyama, 2004; Siddiqi et al., 1995) which were hampered by small heterogeneous study populations and underpowered statistical analyses, so that the role of ICP in neurodevelopment in trigonocephalic patients remained unclear. It is possible that, in especially SSC, the mechanical forces between skull and brain are not strong enough to compromise neuronal oxygenation. Alternatively, the compensatory growth mechanisms of the skull (also without surgery) might be sufficient to prevent interference with cognitive development due to growth restriction of the skull.

*Secondary deformation theory (**second hypothesis**)*

An alternative pathway towards cognitive problems in patients with craniosynostosis implies that deformation of brain matter secondary to synostosis could cause distress in cortical connectivity, ultimately creating functional changes in the way the brain processes information (Aldridge, Marsh, Govier & Richtsmeier, 2002; Carmel, Luken & Ascherl, 1981; Lin et al., 2006). For this research question we focused on the sample of patients with trigonocephaly alone. However, the results showed no association between severity of the frontal stenosis of patients with trigonocephaly and IQ scores. These results were in line with three earlier studies (Mendonca et al., 2009; Starr et al., 2010; Warschausky et al., 2005) that also reported no significant association between skull deformation and cognitive outcome in patients with trigonocephaly. In contrast, Bottero et al. (1998) suggested that severe frontal stenosis of the skull in patients with trigonocephaly was associated with cognitive and behavioral problems. However, in that study, unclear inclusion/exclusion criteria could have led to selection bias; moreover, the use of non-validated parental interviews weakens the validity of their results and may have biased their outcome, resulting in overrated negative parental judgment of (especially) patients with severe frontal stenosis.

Thus, although there are indications that, in children with trigonocephaly, the brain is deformed (Aldridge et al., 2005) and the prevalence of cognitive problems are higher than in the most common form of SSC (Speltz et al., 2015) (i.e. sagittal synostosis), deformation of brain matter is not associated with cognitive problems. Theoretically, compensatory mechanisms (such as plasticity) might have prevented cognitive decline (Kolb, Mychasiuk, Williams & Gibb, 2011). Alternatively, deformation of brain matter secondary to synostosis might cause distress in cortical connectivity. Future research using state-of-the-art techniques (e.g., functional magnetic resonance imaging, or diffusion tensor imaging) are needed to further investigate the possible compensatory mechanisms of brain deformation in trigonocephaly.

*Primary brain anomalies (**third hypothesis**)*

A third potential pathway to explain the association between craniosynostosis and cognitive problems is that both cognitive problems and craniosynostosis originate from a shared primary malformation of the central nervous system (Kjaer, 1995). To test this hypothesis we focused on patients with trigonocephaly alone, since these patients are considered to be at increased risk for intellectual disability, especially those with additional extracranial congenital anomalies (e.g. extra finger; ear or cardiac defects) (Lajeunie et al., 1998; Sidoti et al., 1996). Moreover, trigonocephaly is also associated with brain anomalies such as ventriculomegaly and corpus callosum anomalies (Aldridge et al., 2005; Bottero et al., 1998; Cinalli et al., 1998). Notably, the actual size (or fluctuation in size) of the lateral ventricles in patients with SSC is not associated with the level of ICP, nor is the presence of papilledema in patients with craniosynostosis (Eide & Fremming, 2003; Florisson et al., 2010). Moreover, Collmann et al. (2005) indicated that widened ventricles in children with SSC, especially trigonocephaly (Collmann, Sorensen & Krauss, 1996), are likely to be linked to coincidental cerebral maldevelopment, or secondary to involution of brain parenchyma. Bottero et al. (1998) were the first to suggest that ventriculomegaly (erroneously indicated as hydrocephalus) was associated with low IQ in their cohort of 76 patients with metopic synostosis. With the outcomes of this thesis, we narrowed this observation to patients with trigonocephaly and with additional extracranial congenital anomalies, because the observed increase in lateral ventricular width had the highest negative impact in this subset of patients. Our model suggested that patients with a 5 percent ventricular width above average and extracranial anomalies have a lower mean IQ score of approximately 25 points. This result supports the observation that children presenting with extracranial congenital anomalies (but without trigonocephaly) are reported to be overrepresented in neurodevelopmental disorders such as schizophrenia, autism, hyperactivity, epilepsy, and intellectual disability (Ismail, Cantor-Graae & McNeil, 2000; Trixler, Tenyi, Csabi, Szabo & Mehes, 1997). Furthermore, from an embryologic point of view, ventriculomegaly can be explained by the transformation of somewhat balloon-shaped into C-shaped lateral ventricles during the outgrowth of the developing cerebral hemispheres. During this period, the hemispheres expand in all directions (Moore, 2013), also growing out into the cavities of the balloon-shaped ventricles, resulting in a relative decrease in ventricular width (Nieuwenhuis, 2008). As a consequence, insufficient outgrowth into the cavities will lead to ventriculomegaly. Besides research showed that ventriculomegaly in craniosynostosis is not associated with raised ICP (Eide, Helseth, Due-Tonnessen & Lundar, 2002; Florisson et al., 2010). Subsequently, we believe that the size of the ventricles in patients with trigonocephaly is likely to reflect the degree of insufficient outgrowth, which is indirectly linked to a primary brain developmental problem.

In general, the extracranial anomalies observed in our study probably have their embryologic basis regulated by the common toolbox of developmental genes resulting in comparable biological mechanisms and developmental principles, related to different time frames and different locations in the body (Luijsterburg, Rozendaal & Vermeij-Keers, 2014). To date, the majority of patients with extracranial anomalies cannot be linked to any known syndrome (Lajeunie et al., 1998). Nevertheless, it seems highly plausible that, in the future, more syndromes will be determined in patients with SSC and with extracranial anomalies. Unfortunately, our subgroup of children with extracranial anomalies was too small to reveal any statistical differences. Nevertheless, it is tempting to consider an association between the low (but not significantly different) IQ score in patients with facial anomalies and the fact that brain and facial development are closely related to each other in utero, because the neural crest (Ten Donkelaar, 2014), face and brain originate from the same (neuro) ectodermal layer (O'Rahilly & Muller, 1989). Therefore, it seems feasible that facial anomalies in combination with intracranial anomalies could coincide with aberrant neurodevelopment. Imaging studies in healthy children show that cognitive function correlates with white matter architecture of different regions in the brain (Nagy, Westerberg & Klingberg, 2004; Schmithorst, Wilke, Dardzinski & Holland, 2005), and imaging studies in craniosynostosis patients show that white matter integrity was altered compared with healthy controls (Beckett et al., 2014; Florisson et al., 2011). Raybaud and Di Rocco (2007) hypothesized that the relationship between craniosynostosis and white matter defects might be caused by the lack of interaction with L1 cell adhesion molecules and the fibroblast growth factor receptor. Notably, nonprogressive ventriculomegaly, or insufficient outgrowth into the cavities of the ventricles, can also be explained by a diffuse lack of white matter, which is associated with cognitive problems (Leviton & Gilles, 1996; Raybaud & Di Rocco, 2007). It is tempting to suggest that a diffuse lack of white matter, reflected by widened lateral ventricles, plays a role in the cognitive dysfunction of patients with trigonocephaly.

Therefore, based on the results of our studies and the literature, we consider it likely that the majority of cognitive problems in craniosynostosis, especially trigonocephaly, originate from a shared primary malformation of the central nervous system. Additional studies combining neuropsychology, genetics and latest imaging methods are needed to further investigate the complex pathophysiological process behind the association between cognitive dysfunction and trigonocephaly.

*Negative effects on cognition related to surgery (**fourth hypothesis**)*

Besides the three hypothesized endogenous factors, recent studies suggest that open craniofacial surgery itself might be a significant exogenous factor behind the association

between craniosynostosis and cognitive dysfunction. Both activation of inflammatory cytokines due to surgery-related tissue damage, as well as cumulative exposure to anesthetics, could eventually result in cognitive dysfunctioning (Cibelli et al., 2010; Ikonomidou et al., 1999; Jevtovic-Todorovic et al., 2003; McAfoose & Baune, 2009; Ohzato et al., 1992; Sakamoto et al., 1994; Terrando et al., 2010).

To test this hypothesis, we assessed whether either surgical procedure time or cumulative exposure to anesthetics were associated with postoperative cognitive functions of children with trigonocephaly. Interestingly, our results show that surgical time in open craniofacial surgery was negatively associated with postsurgical cognitive functioning (years later), specifically with the IQ score. To minimize the risk of confounding by indication, we corrected for potential confounding factors, including correction for phenotypic severity. In contrast, no significant association was found between cumulative exposure to anesthetics and cognitive functioning.

Until now, multiple clinical studies have examined whether cognitive development is deleteriously influenced by surgery in young children (Creeley, 2016). Two studies [Pediatric Anesthesia Neurodevelopment Assessment (PANDA) (Davidson et al., 2016) and the General Anesthesia compared to Spinal anesthesia (GAS) trial (Sun et al., 2016)] both suggest that the impact of short exposure to anesthetics (<85 min) early in life on cognition is limited (although the GAS study is still ongoing). However, the latter studies mainly investigated *minor* surgical procedures. Meanwhile, (pre)clinical studies show that the expected minimal threshold for excessive neuronal apoptosis by exposure to anesthetics is rated above 2 hours (Shen et al., 2013; Stratmann et al., 2014; Wilder et al., 2009). Thus, cumulative exposure to anesthetics (>2 h) may well have a negative impact on cognitive functioning. Moreover, particularly in open cranial vault surgical procedures, the amount of inflammatory cytokine release is expected to be much higher compared with that in shorter interventions (Jevtovic-Todorovic et al., 2003).

In this thesis we observed a significant negative association between surgical operating time and cognitive functioning. This result was independent of cumulative exposure to anesthetics, for which no significant association was found with cognitive outcome. Similar to our results, Nauman et al. (2012) also found a negative association between surgery time and cognition; however, their outcome was non-significant. It is possible that the smaller number of patients in their subgroup exposed to open cranial vault surgery might have underpowered their outcome.

Theoretically, a negative association between open cranial vault surgery and cognition might be attributed to the close proximity of the brain to the site of the invasive procedure. In particular, cytokine concentrations are roughly 100 times greater in the area closely

surrounding a surgical wound (Jevtovic-Todorovic et al., 2003). Furthermore, several cytokines (including IL-1, IL-6 and TNF-alpha) are known to permeate the blood-brain barrier using satiable transport systems (Banks, 2005).

Thus, the results of this thesis indicate that surgical operating time in open cranial vault surgery in children under 2 years of age was negatively associated with postoperative cognitive functioning. The extent to which also exposure to anesthetics independently predicts postsurgical cognitive functioning in open cranial surgery remains unclear. However, the present results indicate that any deleterious impact of exposure to anesthetics on postoperative cognitive functioning is likely to be smaller than that of surgical operating time in open cranial vault surgery. Additional multicenter studies are required to confirm these findings, to determine additional potential risk factors, and to explore the possibility of identifying clinically relevant protective factors.

LIMITATIONS AND STRENGTHS OF THE PRESENT RESEARCH

Limitations

Factors that may influence internal validity: First, all patients included in our studies had undergone frontosupraorbital advancement and remodeling aimed at minimizing the development of high ICP. Although it was not demonstrated that this specific surgical procedure might affect cognitive functioning, we cannot exclude the possibility that this surgical intervention did affect the results of this study.

Second, the methodological design of the studies in this thesis does not allow to draw any conclusions about causation. Thus, although we controlled for many potential confounders (especially in Chapter 6), we cannot rule out residual confounding by unknown factors.

Finally, although the association between postoperative IQ score (the most standardized measure of cognitive function) and surgical time is compelling, a within-subject analysis was not possible with our study design, since surgery was performed at an average age of 11 months, when assessment of IQ is known to have poor reliability (Roze et al., 2010).

Factors that may influence external validity: First, the low prevalence of the individual subtypes of craniosynostosis made it impossible to determine the risk of behavioral problems in these separate groups.

Second, although we present one of the largest samples of patients with trigonocephaly worldwide, also in this group the absolute number of participants was relatively small. Consequently, our analyses probably suffered from low statistical power due to the small number of patients in each subgroup. This might have hampered the detection of more

subtle differences in psychopathology between trigonocephalic patients with average and high levels of cognitive functioning, and normative individuals.

Strengths

In addition to the limitations described above, the present research also has several strengths.

First, the use of validated instruments to assess cognitive as well as emotional and behavioral functioning, resulted in comparable data, lowering the risk of information bias.

Secondly, especially in the prospective data on trigonocephaly, there was an impressive 94 percent participation rate; this was combined with information on those patients who decided not to participate, thereby limiting possible selection bias.

Third, since the Dutch Craniofacial Center of the Erasmus University Medical Center in Rotterdam treats approximately 70 percent of all craniosynostosis patients in the Netherlands (Kweldam, van der Vlugt & van der Meulen, 2011), this makes the data representative for the national situation.

Fourth, when describing behavioral and emotional problems, we controlled for the IQ score. This resulted in a better comparison of the prevalence of behavioral and emotional problems of children both with, and without craniosynostosis.

Finally, the use of independent and routinely available variables makes it easier to effectively reproduce our studies.

Clinical Implications

Although results from observational studies, such as presented in this thesis, do not allow to draw conclusions about causality, they offer new insights into the strength of associations between craniosynostosis, especially trigonocephaly, and cognitive, emotional and behavioral problems, and the potential mechanisms explaining these associations.

When children with trigonocephaly present with extracranial anomalies, they should be monitored closely by specialized professionals with regard to the development of cognitive, behavioral and/or emotional problems, in order to counteract treatment delays and insecurity by caregivers about their child's behavior.

Parents should be informed that, when children with craniosynostosis have a normal cognitive development, they may not be at greater risk of emotional and/or behavioral problems compared to healthy children.

If robust evidence from future studies indicates that exacerbated inflammation in brain is related to open cranial vault surgery, then new ways might be found to counter-regulate the deleterious effects of exacerbated inflammation (Terrando et al., 2013). Subsequently, future systemic prophylaxis may help to prevent the potential negative effects of surgery-

induced activation of inflammatory cytokines in children exposed to cranial vault surgery. In addition, endoscopic techniques in craniosynostosis might be an appropriate alternative to open surgery, as studies on these techniques show significantly shorter surgical operating time and less blood loss, as compared to open surgery (Thompson et al., 2018).

CHALLENGES FOR THE FUTURE

The present thesis offers new insights into the strength of associations between craniosynostosis, especially trigonocephaly, and cognitive, emotional and behavioral problems, and in potential mechanisms behind these associations. Nevertheless, especially the findings on the mechanisms behind cognitive, behavioral and emotional problems, do not allow any conclusions to be drawn about causality. Nevertheless, based on our results, it seems likely that cognitive problems in single-suture craniosynostosis, especially trigonocephaly, originate from a shared primary malformation of the central nervous system. Moreover, open cranial vault surgery itself might also result in loss of cognitive function. However, more robust evidence is needed to strengthen these conclusions.

First: multicenter studies with larger samples are needed to overcome the power problems we experienced in investigating the prevalence of cognitive, behavioral and emotional problems in the subtypes of craniosynostosis. Moreover, such studies might reveal more subtle differences in psychopathology between trigonocephalic patients with average and high levels of cognitive functioning and normative individuals.

Second: to strengthen the hypothesis that cognitive problems in craniosynostosis are caused by problems in white matter integrity, state-of-the-art imaging studies on associations between diffusion-tensor imaging and cognitive outcome in craniosynostosis could be the next step to investigate this potential relation.

Third: if integrity of white matter proves to be a significant factor in the association between craniosynostosis and cognitive problems, genetic studies on the origin of white matter integrity will be required. Based on the review of Raybaud et al., future studies should focus on the interaction between the L1 cell adhesion molecule and fibroblast growth factor receptors (Raybaud & Di Rocco, 2007).

Fourth: direct associations between cytokine concentrations before, during and after cranial vault surgery of especially IL1, IL6 and TNF-alfa and cognitive outcome, might serve to strengthen our proposed negative relationship between cognition and open cranial vault surgery in craniosynostosis.

Lastly: on a clinical level, studies comparing cognitive outcome between open and endoscopic cranial vault surgery might provide more insight in the association between invasive versus less invasive surgery, and cognitive outcome.

GENERAL CONCLUSIONS

The relationship between craniosynostosis and behavioral problems is likely to be mediated by the IQ score. Lower IQ scores are associated with more behavioral and emotional problems, as is also the case in the general population. Findings on possible mechanisms behind cognitive problems in children with craniosynostosis indicate a less prominent role of mechanical pressure between the skull and its content in the association between craniosynostosis and cognitive problems. Moreover, changes in brain morphology, such as frontal stenosis in trigonocephaly, are unlikely to be the basis of the higher prevalence of cognitive problems. Instead, the findings of this thesis indicate that cognitive problems in single-suture craniosynostosis, especially trigonocephaly, originate (at least partly) from primary brain problems. Moreover, there is a possibility that longer exposure to open cranial vault surgery is associated with lower IQ scores in these children.

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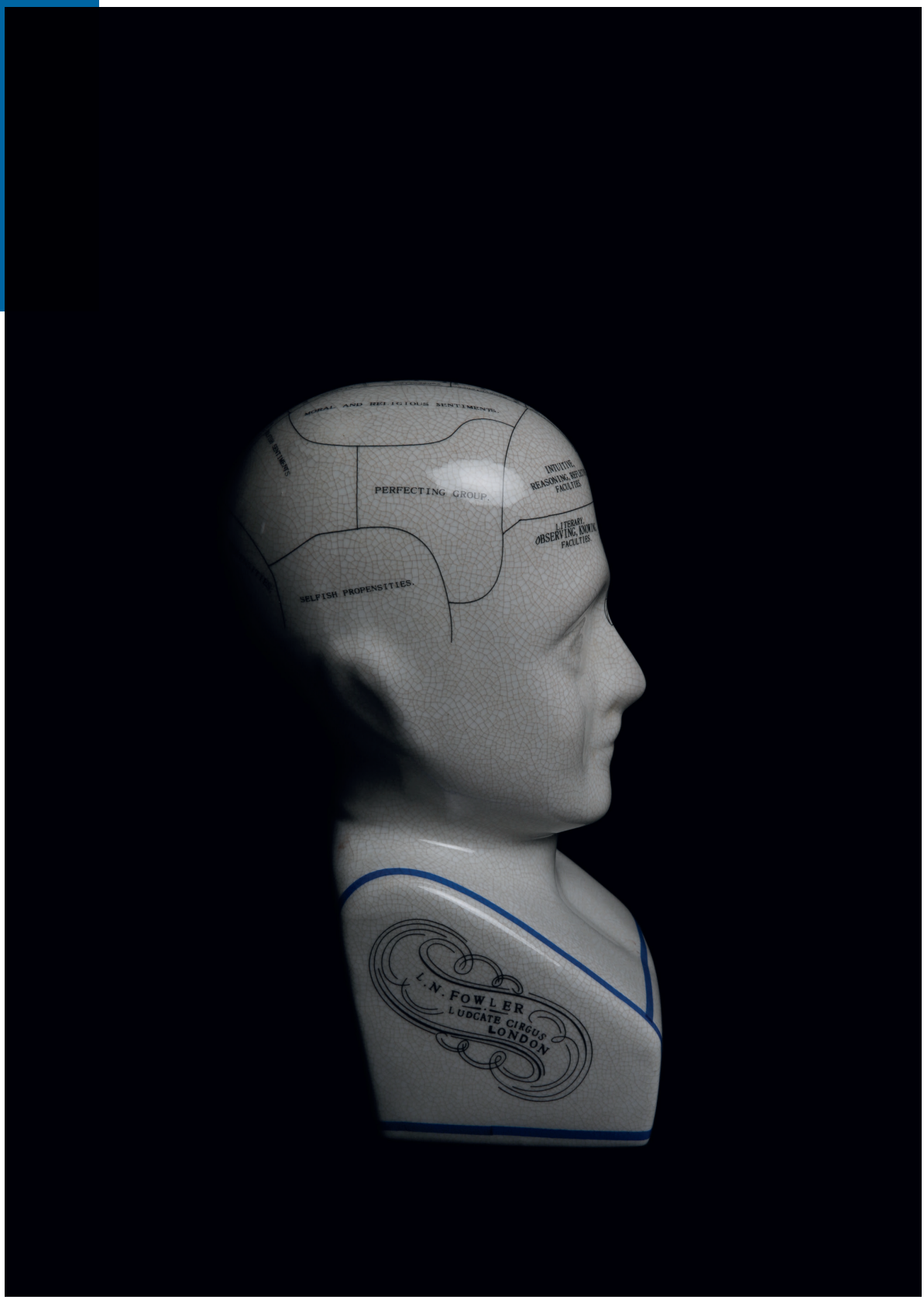
MORAL AND RELIGIOUS SENTIMENTS.
PERFECTING GROUP.
SELFISH PROPENSITIES.
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CHAPTER 8

SUMMARY || SAMENVATTING

SUMMARY

Craniosynostosis is a congenital condition that involves the premature fusion of one or more of the fibrous sutures connecting the bones of a child's skull. This condition can result in restricted growth perpendicular to the affected suture and compensatory growth in unfused bony plates, producing an altered head shape. In addition, craniosynostosis is associated with cognitive, behavioral and emotional problems. To date, however, the mechanisms behind these associations remain unclear.

The main research questions of this thesis - which is divided into two parts - are outlined in the general introduction (**Chapter 1**).

Part 1 reports the prevalence of (neuro)cognitive, behavioral and emotional problems in children with craniosynostosis, with additional focus on children with trigonocephaly, using validated instruments and taking intelligence level (i.e. intelligence quotient; IQ scores) into account. For this, three specific items were investigated.

Research questions:

- What is the prevalence of (neuro)cognitive, behavioral and emotional problems in different types of craniosynostosis?
- Are these problems more prevalent in children with craniosynostosis compared to the general population?
- Is intellectual disability a mediating factor in the association between emotional and behavioral problems in craniosynostosis, as it is in the general population?

In **Part 2** the aim was to extend the existing knowledge on the etiology of cognitive problems in children with craniosynostosis. For this, four hypotheses related to cognitive function were examined.

Research questions to assess the association between intracranial pressure and cognitive functioning *(**first hypothesis**)*:

- Is the quantity of preoperative beaten-copper skull patterns in patients under 18 months of age with craniosynostosis associated with postoperative cognitive functioning?
- Is preoperative skull size in patients with craniosynostosis associated with postoperative cognitive functioning?

Research question to assess the association between skull deformation and cognitive functioning *(**second hypothesis**):*

- Is the preoperative severity of frontal stenosis in patients with trigonocephaly associated with postoperative cognitive functioning?

Research questions to assess the association between primary brain deformation and cognitive functioning ***(third hypothesis)***

- Are primary brain anomalies associated with cognitive functioning in patients with trigonocephaly?
- Is the width of the central part of the lateral ventricles associated with cognitive functioning in patients with trigonocephaly?

Research questions to assess the association between open surgical treatment and cognitive problems ***(fourth hypothesis)***

- Is duration of surgery of patients exposed to cranial vault surgery associated with postoperative cognitive functioning?
- Is cumulative exposure to anesthetics in patients exposed to cranial vault surgery associated with postoperative cognitive functioning?

Data used in this thesis were derived from two groups of patients. The first sample comprised a heterogeneous group of patients with craniosynostosis: described in **Chapters 2 and 4**. This sample consisted of the data of 138 patients (83 males, 55 females) from the National Craniofacial Unit of the Erasmus Medical Center in Rotterdam. This sample was part of a larger cohort originally collected by Dr. J. M. E. Okkerse. The inclusion criteria for this study were: diagnosed with craniosynostosis, aged between 5 and 16 years, and Dutch as the native language. All patients in this cohort were born between 1978 and 1992. Depending on additional inclusion criteria (as described in Chapters 2 and 4) the number of patients can vary per study.

The second sample consisted of a group of patients with only trigonocephaly: described in **Chapters 3, 5 and 6**. The sample comprised 82 patients with trigonocephaly, aged 4 to 18 years, from the National Craniofacial Unit of the Erasmus Medical Center. Inclusion criteria for this study were: a diagnosis of metopic synostosis confirmed on a three-dimensional CT scan, and Dutch as the native language. All patients meeting the inclusion criteria were born between 1990 and 2006. Depending on additional inclusion criteria (as described in Chapters 3, 5 and 6) the number of patients can vary per study.

In order to address the research questions presented in **Part 1**, we investigated the prevalence of cognitive, behavioral and emotional problems in a group of patients with different types of craniosynostosis, as well as in a group of patients with solely trigonocephaly **(Chapters 2 and 3)**.

In **Chapter 2** we retrospectively determined the prevalence of behavioral and emotional problems in 115 patients with different types of craniosynostosis from the Erasmus Medical Center-Sophia Children's Hospital in Rotterdam. Subsequently, we investigated the effect of

intelligence level (IQ scores) on behavioral and emotional problems in these different types of craniosynostosis. The main results suggested that, when intelligence level is taken into account, craniosynostosis is not associated with an increased risk of behavioral or emotional problems, or with the type of craniosynostosis.

In **Chapter 3** we prospectively assessed behavioral and emotional problems in 82 patients aged 4 to 18 years with trigonocephaly, using validated instruments, and taking IQ scores into account. In addition, in this same group of patients, we examined the percentage with intellectual disability, as well as associations between IQ scores and extra-cranial anomalies. The outcomes were in line with the results found in Chapter 2, indicating that the relatively high prevalence of behavioral problems in patients with trigonocephaly seem mainly attributable to the co-occurrence of trigonocephaly and low intelligence.

The aim of **Part 2** was to extend current knowledge on the etiology underlying cognitive problems in patients with craniosynostosis. For this, we investigated four hypotheses (outlined above) which are suggested to play a role in the association between (neuro) cognitive, behavioral and emotional problems, and craniosynostosis.

Chapter 4 examined the association between preoperative beaten-copper skull patterns (before age 18 months; assessed on 538 skull radiographs of 95 children with craniosynostosis) and postoperative IQ scores, focusing on the hypothesis that increased mechanical pressure between the skull and its content (brain, blood, and spinal fluid) is the basis for cognitive problems in craniosynostosis (**first hypothesis**). Skull radiographs, on which the percentage of beaten-copper skull patterns was assessed, were made at a mean age of 1.2 years, whereas the IQ assessment was performed at a mean age of 8.4 years. Results showed a relatively high preoperative incidence of beaten-copper skull patterns (71.6%) before age 18 months. Moreover, the amount of beaten-copper skull patterns increased during the period of rapid brain expansion in the first three years of life. However, no significant association was found between the location or percentage of beaten-copper skull patterns and IQ score later in life.

In **Chapter 5** we prospectively investigated 72 patients with trigonocephaly based on three hypotheses related to the association between craniosynostosis and cognitive problems (**the first, second and third hypotheses**). With reference to the first hypothesis, investigation of preoperative skull size before age 6 months and postoperative IQ score revealed no significant association between skull size and IQ score. Then, to investigate the hypothesis that skull deformation is the basis for cognitive problems in craniosynostosis (***second hypothesis***), CT scans were evaluated to check for an association between preoperative frontal stenosis and postoperative IQ score. Results showed no significant association between skull deformation and IQ score. Finally, we assessed whether primary brain anomalies in patients with trigonocephaly are associated with later cognitive functioning (***third hypothesis***),

focusing on the hypothesis that primary brain problems are the common cause of both cognitive problems and craniosynostosis. Results showed that the width of the central part of the lateral ventricles, and an interaction effect between width of the central part of the lateral ventricles and extracranial anomalies, had a significant negative association with postoperative IQ score. This outcome tends to support the third hypothesis, that primary brain disorders affect the development of cognitive problems in trigonocephaly.

Moreover, **Chapter 6** addressed the potential association between either duration of surgery or cumulative exposure to anesthetics in patients with trigonocephaly, by examining whether open cranial vault surgery itself is related to cognitive dysfunction in patients with trigonocephaly (***fourth hypothesis***). The postoperative IQ score and the Visual-Motor Integration (VMI) score were prospectively examined in 52 consecutive patients with metopic synostosis (from the Dutch Craniofacial Center of Erasmus University Medical Center), who underwent a cranial vault procedure before age 2 years. Data on duration of surgery and cumulative anesthetic concentrations were retrospectively assessed from the patient files. Outcomes suggested a significant negative correlation between duration of surgery and postoperative IQ score, whereas no significant correlation was found between cumulative exposure to anesthetics and either IQ score or VMI score. The negative association between duration of surgery and IQ score was independent of the cumulative exposure to anesthetics.

Finally, in **Chapter 7,** the main findings and conclusions from emerging from Chapters 2 to 6 are presented and discussed, implications for clinical practice are addressed, and some recommendations are made for future research.

SAMENVATTING

Craniosynostosis is een congenitale afwijking waarbij de schedelnaden tussen de botplaten in de ontwikkelende schedel te vroeg sluiten. Als gevolg hiervan ontstaat een afname van schedelgroei loodrecht op de te vroeg gesloten schedelnaad alsook een compensatoire groei vanuit nog geopende nabijgelegen schedelnaden. Dit leidt tot een afwijkende schedelvorm. Hiernaast is craniosynostosis ook geassocieerd met zowel cognitieve, gedragsmatige als emotionele problemen. Tot op heden zijn de mechanismen achter deze associaties nog niet bekend.

De onderzoeksvragen van het huidige proefschrift, welke is opgedeeld in twee delen, worden besproken in de algemene introductie **(hoofdstuk 1)**.

Deel 1 van het proefschrift beschrijft de prevalentie van (neuro)cognitief, gedragsmatig en emotionele problemen bij kinderen met craniosynostosis. Dit is op een gevalideerde manier gemeten waarbij we rekening hebben gehouden met het intelligentieniveau van de patiënten (intelligentiequotiënt; IQ-score). Bijkomend is er specifiek gekeken naar kinderen met een trigonocephalie.

Onderstaand de drie specifieke onderzoeksvragen die we in deel 1 hebben onderzocht.

Onderzoeksvragen:

- Wat is de prevalentie van (neuro)cognitive, gedragsmatige en emotionele problemen in verschillende vormen craniosynostosis?
- Komen deze problemen meer voor dan in de algemene bevolking?
- Is een verstandelijke beperking een mediërende factor bij de gedrags- en emotionele problemen in craniosynostosis, zoals dat ook geldt in de algemene bevolking?

Het doel van **deel 2** van het proefschrift is om de kennis te vergroten naar de etiologie van cognitieve problemen bij kinderen met craniosynostosis. Er zijn in dit onderdeel vier hypotheses naar de oorzaak van cognitieve problemen bij craniosynostosis onderzocht.

Hypotheses die de associatie tussen intracraniale druk en cognitief functioneren toetsen ***(eerste hypothese)***:

- Is de kwantiteit van preoperatief beaten-copper pattern in de schedel voor de leeftijd van 18 maanden geassocieerd met postoperatief cognitief functioneren?
- Is de preoperatieve schedelgrootte bij patiënten met craniosynostiosis geassocieerd met postoperatief cognitief functioneren?

Hypothese die de associatie tussen schedeldeformatie en cognitief functioneren toetst ***(tweede hypothese)***:

- Is de preoperatieve ernst van de frontale stenose bij patiënten met trigonocephalie geassocieerd met postoperatief cognitief functioneren?

Hypotheses die de associatie tussen primaire hersendeformatie en cognitief functioneren toetsen ***(derde hypothese)***:

- Zijn primaire hersenanomalieën geassocieerd met cognitief functioneren bij patiënten met een trigonocephalie?
- Is de wijdte van het centrale deel van de laterale ventrikels geassocieerd met cognitieve functioneren bij patiënten met een trigonocephalie?

Hypotheses die de associatie tussen open chirurgische behandeling en cognitief functioneren toetsen ***(vierde hypothese)***:

- Is de duur van de snijtijd van de open chirurgische procedure bij patiënten met craniosynostosis geassocieerd met postoperatief cognitieve functioneren?
- Is de cumulatieve blootstelling aan anesthetica tijdens de chirurgische procedures van patiënten met craniosynostosis geassocieerd met postoperatief cognitief functioneren?

Data die is gebruikt in het huidige proefschrift is afkomstig uit twee onafhankelijke patiënten samples. De eerste sample bevat een heterogene groep van patiënten met craniosynostosis: beschreven in **hoofdstuk 2 en 4**. Deze sample bestaat uit data van 138 patiënten (83 jongens en 55 meisjes) van de nationale craniofaciale afdeling van het Erasmus Medisch Centrum in Rotterdam en was onderdeel van een groter cohort dat origineel is verzameld door Dr. J.M.E. Okkerse. De inclusiecriteria voor deze studie waren: gediagnostiseerd zijn met craniosynostosis, leeftijd tussen de 5 en de 16 jaar en Nederlands als moedertaal. Alle patiënten in dit cohort zijn geboren tussen 1978 en 1992. De patiënten samples kunnen per studie variëren, afhankelijk van aanvullende inclusiecriteria (zoals beschreven in hoofdstuk 2 en 4).

De tweede sample bestaat uit een groep patiënten waarin alleen kinderen met trigonocepahlie zijn geïncludeerd: beschreven in **hoofdstuk 3, 5 en 6**. Deze sample bevat 82 patiënten met trigonocepahlie, tussen de 4 en 18 jaar oud, van de nationale craniofaciale afdeling van het Erasmus Medisch Centrum in Rotterdam. De inclusiecriteria voor deze studie was: een metopicanaad stenose aangetoond middels een driedimensionale CT-scan en Nederlands als moedertaal. Alle patiënten die voldeden aan de inclusiecriteria zijn geboren tussen 1990 en 2006. De patiënten samples kunnen per studie variëren, afhankelijk van aanvullende inclusiecriteria (zoals beschreven in hoofdstuk 3, 5 en 6).

Om de onderzoeksvragen zoals beschreven in **deel 1** te onderzoeken hebben we gekeken naar de prevalentie van zowel cognitieve, gedragsmatige als emotionele problemen bij een groep patiënten met verschillende vormen van craniosynostosis, alsook in een groep met alleen kinderen met trigonocephalie **(hoofdstuk 2 en 3)**.

In **hoofdstuk 2** hebben we retrospectief onderzocht wat de prevalentie is van gedrags- en emotionele problemen bij 115 patiënten met verschillende vormen van craniosynostosis onder behandeling van het Erasmus Medisch Centrum-Sophia Kinderziekenhuis in Rotterdam. Vervolgens hebben we onderzocht wat de invloed van het intelligentieniveau (IQ-scores) is op gedrags- en emotionele problemen bij deze verschillende vormen van craniosynostosis. De uitkomst suggereert dat, als we rekening houden met het intelligentieniveau, craniosynostosis niet geassocieerd is met een toename van het risico op gedrags- of emotionele problemen.

In **hoofdstuk 3** hebben we prospectief, met gevalideerde instrumenten en rekening houdend met IQ-scores, onderzocht wat de prevalentie is van gedrags- en emotionele problemen bij 82 kinderen met trigonocephalie in de leeftijd tussen 4 en 18 jaar oud. Bijkomend hebben we in dezelfde studiegroep het percentage verstandelijke beperking alsook de associatie tussen verstandelijke beperking en extra-craniale anomaliteiten onderzocht. De uitkomsten zijn in lijn met de uitkomsten gevonden in hoofdstuk 2, en geven de suggestie dat het relatief hoge percentage gedragsproblemen van kinderen met trigonocephalie toe de schrijven is aan het hoge percentage verstandelijke beperking in deze groep.

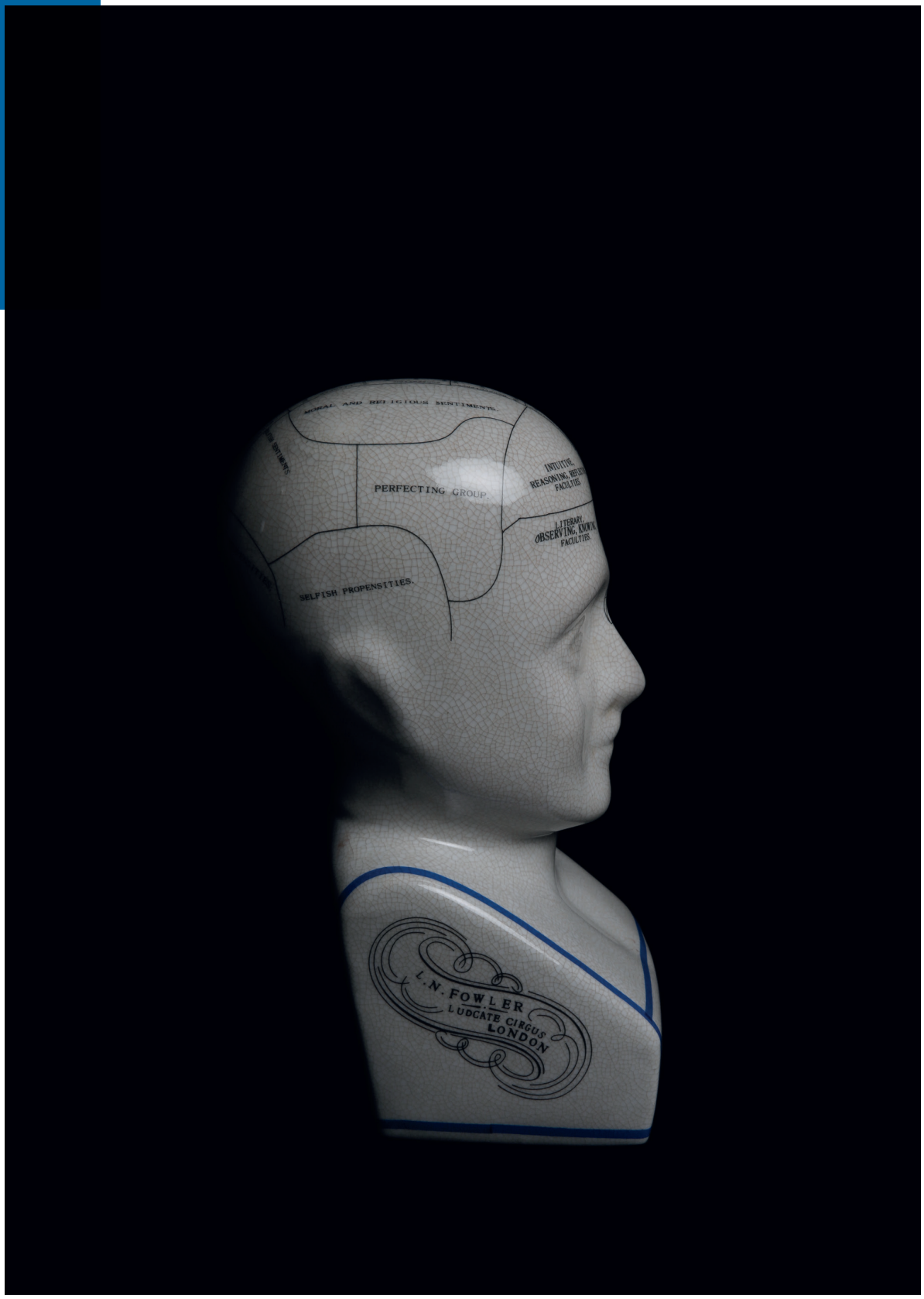
Het doel van **deel 2** van het proefschrift is het uitbreiden van de huidige kennis over de etiologie achter de cognitieve problemen bij patiënten met craniosynostosis. Hiervoor hebben we vier hypotheses onderzocht (zoals boven beschreven) die gesuggereerd worden een rol te spelen in de associatie tussen zowel (neuro)cognitief, gedragsmatig- als emotionele problemen en craniosynostosis.

In **hoofdstuk 4** onderzoeken we de associatie tussen preoperatief beaten-copper pattern in de schedel (voor de leeftijd van 18 maanden; onderzocht in 538 schedel röntgenfoto's van 95 kinderen met craniosynostosis) en postoperatieve IQ-scores. Hierbij ligt de focus op de hypothese dat verhoogde mechanische druk tussen de schedel en haar inhoud (hersenen, bloed en hersenvocht) de basis is voor de cognitieve problemen bij craniosynostosis (**eerste hypothese**). Zowel het percentage beaten-copper pattern op schedel röntgenfoto's (gemiddelde leeftijd 1.2 jaar) als een intelligentieonderzoek op de leeftijd van gemiddeld 8.4 jaar zijn in kaart gebracht. De resultaten laten een relatief hoge prevalentie (71.6%) van beaten-copper pattern voor de leeftijd van 18 maanden zien. Ook is er aangetoond dat het beaten-copper pattern toeneemt gedurende de periode van versnelde hersengroei in de eerste drie levensjaren. Echter er zijn geen significante associaties gevonden tussen de locatie noch het percentage beaten-coppern pattern en IQ-score op latere leeftijd van de onderzochte patiënten.

In **hoofdstuk 5** hebben we bij 72 patiënten met trigonocephalie prospectief drie hypotheses over de associatie tussen craniosynostosis en cognitieve problemen onderzocht (de **eerste, tweede en derde hypothese**). Verwijzende naar de eerste hypothese, hebben we onderzocht of de grootte van de schedel op de leeftijd van 6 maanden geassocieerd is met de postoperatie IQ-score. Uitkomsten laten geen significante associatie zien tussen schedelgrootte en IQ-score. Verwijzend naar de hypothese dat schedeldeformatie geassocieerd is met cognitief functioneren, hebben we onderzocht of er associaties gevonden zijn tussen de mate van deformatie en cognitief functioneren (**tweede hypothese**). Om dit te onderzoeken zijn potentiële associaties tussen de preoperatieve frontale stenose (gemeten middels CT-scans) en postoperatieve IQ-scores gemeten. Uitkomsten laten geen significante relaties zien tussen de mate van frontale stenose en IQ-scores. Tenslotte hebben we associaties onderzocht tussen primaire hersenafwijkingen bij kinderen met een trigonocephalie en hun postoperatieve cognitief functioneren **(derde hypothese)**. Bij deze onderzoeksvraag hebben we ons gefocust op de hypothese die stelt dat primaire problemen in de hersenen een rol spelen bij zowel de cognitieve problemen als de craniosynostosis. De resultaten laten zien dat de wijdte van het centrale deel van de laterale ventrikels significant negatief geassocieerd is met IQ-score bij met name patiënten met extracraniale anomaliteiten. Deze uitkomst suggereert de derde hypothese te ondersteunen, waarin wordt gesteld dat primaire hersenstoornissen de ontwikkeling van cognitieve problemen bij trigonocephalie beïnvloeden.

In **hoofdstuk 6** is de potentiele associatie tussen zowel de duur van chirurgie als de cumulatieve blootstelling aan anesthesie bij patiënten met trigonocepalie behandeld. Hierin hebben we onderzocht of een open chirurgische behandeling van craniosynostosis mogelijk geassocieerd is met cognitief disfunctioneren bij patiënten met trigonocephalie **(vierde hypothese)**. Zowel de postoperatieve IQ-score als de Visueel-Motorische Integratie (VMI) score werd prospectief gemeten bij 52 patiënten van de nationale craniofaciale afdeling van het Erasmus Medisch Centrum in Rotterdam. Alle patiënten zijn blootgesteld aan een open chirurgische behandeling voor hun metopicanaad stenose voor de leeftijd van 2 jaar. Data over de duur van de chirurgische procedure alsook van de cumulatieve dosering anesthesie zijn retrospectief verzameld uit het elektronisch patiëntendossier. De resultaten suggereren een significante negatieve relatie tussen de duur van de chirurgische procedure en postoperatieve IQ-score, terwijl er geen significante relatie is gevonden tussen de cumulatieve blootstellig aan anesthesie en IQ-score of VMI-score. Notabene, de negatieve associatie tussen duur van de chirurgie en IQ-score is onafhankelijk van de cumulatieve blootstelling aan anesthesie.

Tenslotte zijn in **hoofdstuk 7** de belangrijkste bevindingen en conclusies uit de hoofdstukken 2 tot 6 gepresenteerd en besproken, implicaties voor de klinische praktijk behandeld en worden enkele aanbevelingen gedaan voor toekomstig onderzoek.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