Brain structure and function in velo-cardio-facial syndrome with and without psychosis
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Citation for published version (APA):

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CHAPTER 1

INTRODUCTION
1.1 Schizophrenia and genetic research
Schizophrenia remains a common, usually lifelong disorder with a strong tendency towards severity, which carries a huge burden for families and carers and brings large costs to the national health service. Many years of research still have not unravelled the complex aetiology and pathogenesis of the illness. Over the last decades there have been numerous genetic studies of schizophrenia; data from family, twin and adoption studies have demonstrated that schizophrenia is determined for a major part by genetic factors, with environmental factors playing an important, though relatively minor role. However, subsequent search for chromosomal loci and candidate genes by using linkage and association studies has proven a difficult task. The reason for this is probably because there are multiple susceptibility genes each with a small effect, which act in conjunction with epigenetic processes and environmental factors. In addition, genetic research in schizophrenia has been complicated by the absence of a diagnostic pathology, other biological markers of the illness, and its clinical heterogeneity. As a result, genetic studies have lacked sufficient power, given inconsistent results and positive results have rarely been replicated. An interesting new opportunity to study the neurobiology of schizophrenia has arisen since velocardio-facial syndrome (VCFS) has been increasingly reported to be associated with schizophrenia. Instead of “searching for the genes for schizophrenia”, studying an identified genetic disorder like VCFS that is associated with a high prevalence of psychopathology could be a challenging alternative approach to the current research strategy.

1.2 Velo-cardio-facial syndrome
VCFS, (22q11 deletion syndrome, Shprintzen syndrome or DiGeorge syndrome), is the most common microdeletion syndrome occurring in approximately 1:4000 live births. The syndrome is associated with a small interstitial deletion at the long arm of chromosome 22 containing several identified genes. The majority of the deletions are de novo but the deletion can be transmitted in 10-15% of cases as an autosomal dominant disorder. Subsequently, individuals with a 22q11 deletion have a 50% risk of having an affected offspring in each pregnancy. In 80-85% of individuals with VCFS an interstitial deletion is detected by fluorescence in situ hybridization (FISH). A fluorescently labeled DNA or RNA probe is hybridized to immobilized metaphase chromosomes prepared from a blood sample (see figure 1). The typically deleted region (TDR) has a length of approximately 3Mb and contains 30-50 genes, the deletion size, however, is variable. Clinically, VCFS is characterised by multiple congenital anomalies affecting a number of tissues and organ systems, many of which are embryologically derived from rostral neural crest cells. It has been suggested that aberrant cephalic neural crest migration to the 3rd and 4th branchial arches may be an important embryologic basis for VCFS. Although considerable phenotypic variability occurs, the most frequently reported clinical features include congenital heart defects, cleft palate, pharyngeal insufficiency, thymus hypoplasia,
hypocalcemia, characteristic facial dysmorphology (wide set eyes, high nasal bridge), and mild / borderline learning disability$^{6,10}$ (figure 2). Since diagnostic testing has become available only relatively recently, many affected individuals that have come to medical attention are children. As a result the existing literature on VCFS has mainly described children with VCFS. In recent years VCFS has received increasing attention in psychiatric research because the people with VCFS are presenting extensive behavioural and psychiatric problems.

Figure 1. Fluorescence in-situ hybridisation
1.3 A (genetic) subtype of schizophrenia?

Children with VCFS frequently have behavioural problems including poor social interaction, attention and concentration problems, and impulsive behaviour. Childhood psychiatric disorders including attention deficit disorders, autistic spectrum disorders, anxiety and affective disorders, are highly prevalent in this group of people but it is not clear if their prevalence is higher than in other people with similar intellectual impairments\textsuperscript{11}. In adult life people with VCFS seem to be particularly at risk for developing psychosis\textsuperscript{12}. However, the interpretation of the scarce literature available on the prevalence of psychosis in VCFS, has been complicated by methodological issues and reported prevalences range from 10 - 64\%\textsuperscript{13-15}. Differences in diagnostic criteria used, small sample sizes, different age ranges used, are all possible explanations for the discrepancy in results. Besides, longitudinal data and suitable control groups are still lacking. Furthermore, it is not clear to what extent the results are specific to VCFS and 22q11 deletion or the consequence of learning disability in general, or a combination of both. However, there is now no doubt that there is an association between VCFS and psychosis, because 1) there is an increased prevalence of psychosis in the VCFS population compared to the general population;
2) there is an increased risk of VCFS in the schizophrenia population compared to the general population; 3) there are suitable candidate genes for psychosis located on 22q11. Basset and Chow (1999) have suggested that VCFS related psychosis may represent a homogeneous genetic subtype of schizophrenia\textsuperscript{15}. Others, debate if the use of the term schizophrenia is justified in this group even though there is no doubt that psychotic symptoms including hallucinations and delusions are highly prevalent in adults with VCFS\textsuperscript{17}. In a recent study the psychiatric phenotype between VCFS associated schizophrenia and non-VCFS associated schizophrenia was compared\textsuperscript{18}. The authors concluded that overall the two groups were nearly indistinguishable; the only difference was significantly less substance abuse and more impulsive behaviour in the group with VCFS. In this thesis the terms schizophrenia and psychosis will be used both and the diagnostic classification will not be discussed any further as this was not the objective of the studies presented in this thesis.

1.4 Brain anatomy and cognitive profile in children with VCFS

The understanding of brain function and development, similar to investigating other neurogenetic or psychiatric conditions, is a necessary step for our understanding of the cognitive, behavioral, and psychiatric phenotype associated with VCFS, and this may contribute to our knowledge on the neurobiology of schizophrenia. The majority of investigations of cognition in VCFS have focused on psychoeducational profiles and communicative skills in children in order to find appropriate remedial approaches to the needs of this group. The findings indicate a complex pattern of areas of strengths and difficulties. Most investigations have focused on the VCFS children's abilities in language and academic performance and report that many children have language abnormalities including immature language usage, poor development of numeric skills and significant impairments in reading and spelling\textsuperscript{10, 14}. Full-scale IQ is generally reported to be in the low-normal to mild learning disability range among school-aged children\textsuperscript{20}. Several studies suggest that children with VCFS have higher mean verbal IQ (VIQ) scores compared to mean performance IQ (PIQ) scores, resembling a non-verbal learning disability profile\textsuperscript{10, 20-23}. Furthermore, it has been found that VCFS children's mathematical skills are more severely impaired than their abilities in reading and spelling\textsuperscript{20}. Additionally, more specific deficits have been found in attention\textsuperscript{24}, executive function\textsuperscript{25} and social cognition\textsuperscript{26}. Specific impairments in attention, memory and social cognition are also particularly significant as they may be risk factors for the development of future psychiatric disorder in VCFS individuals. Although the aims are to describe a unique cognitive profile due to a 22q11 deletion one has to acknowledge that as with most other developmental disorders there are and will invariably be a considerable phenotypic variability within the group. this can be due to origins as varied as developmental, prenatal, familial or experiential factors. Hence, it is important to explore this syndrome in accordance with strict methodologies using appropriate tests, homogenous groups, large sample sizes and suitable control groups. In the literature there has been a striking lack of suitable control groups matched for IQ, and many investigations have also had ascertainment bias and small sample sizes. However, since the majority of studies of VCFS have been performed in the last
years this is a relatively new and exciting area to research and the above mentioned limitations have been observed by all authors. Hence, the future will hopefully shed more lights on the complexities of cognition in VCFS and the studies in this thesis have tried to overcome some of the above mentioned obstacles.

Early neuroimaging reports emphasized qualitative differences in brain structures associated with VCFS\(^{25}\). In addition to the observation of overall brain and cortical atrophy, a high prevalence of midline defects like small corpus callosum, cavum septum pellucidum or cavum vargae, enlarged ventricules, cysts adjacent to the frontal horns of the ventricles, small posterior fossa and vermal atrophy, and white matter hyperintensities (WMHs) have been described\(^{25-28}\).

In addition, several cases of cortical dysgenesis including uni/bilateral fronto-parietal polymicrogyria have been reported in children with VCFS\(^{29-33}\), possibly resulting in hemiplegia and seizures in the most severely affected patient. However, still it remains unclear what the underlying pathogenetic mechanism for VCFS associated cortical dysgenesis is. Abnormal neuronal migration is one proposed explanation, but vascular disruption has also been suggested as a potential mechanism\(^{31, 34}\). Classification of polymicrogyria depends on histological characterization (unlayered vs. four-layered) reflecting early (10-18\(^{\text{th}}\) week of gestation) or later (13-24\(^{\text{th}}\) week of gestation) developmental disorder\(^{35}\).

Only few studies have investigated quantitative volumetric changes in children and adolescents with VCFS. The first study published\(^{36}\) reported that children with VCFS experience: 1) a decrease in overall brain volume due to diminution in volumes of both cerebral grey and white matter; 2) a relative enlargement of the frontal lobe after adjusting for total brain volume. 3) a decrease in tissue volume in the left parietal lobe primarily attributable to disproportionate reduction of grey matter in this region, 4) a decrease in right cerebellar tissue volume due to a disproportionate reduction in white matter for this area. Another group found white matter reduction in the posterior brain regions (parietal and occipital lobes) and VCFS compared to controls\(^{37}\). Kates et al. also observed an association between full-scale IQ and total cerebral tissue in both groups which emphasizes the importance for using IQ matched control groups in neuroimaging studies something which both groups failed to do.

Thusfar our knowledge on brain function and development in VCFS is based on relatively few studies that have been carried out in children and adolescents. The literature suggests that specific cognitive impairments and structural brain anomalies are present in children and adolescents with VCFS. To what extent these play a role in the development of psychosis in adulthood in this population is not yet known as longitudinal data and studies in adults with VCFS are lacking.

1.5 Objectives and methods

'What can we learn from VCFS on the aetiology and pathogenesis of psychosis?', was the main rationale behind the studies described in this thesis. More specifically
we wished to explore the neuropsychological and anatomical correlates that are associated with a chromosome 22q11 deletion and how these could be affected by the presence of psychosis. To study the neuropsychological profile in adults with VCFS we used a comprehensive test battery that was considered suitable for a population with learning disability. The battery was chosen in such a manner that it would not take too much time, in other words a battery that would be realistic to carry out in a learning disabled population. On the other hand, intellectual ability, visuospatial function, memory, executive function and attention were the cognitive domains we wished to include in the test battery. We tested adults with VCFS, and a control group of similar intellectual ability (chapter 3). Subsequently we compared psychotic and non-psychotic individuals with VCFS (chapter 5).

To study brain anatomy we used magnetic resonance imaging (MRI) using a GE 1.5 Tesla (indicating the strength of the magnetic field) scanner. Clinical MRI relies on the capacity of most organic tissue, when placed into a magnetic field, to absorb energy from an external source (e.g. radio waves) and then re-emit this energy, to be picked up as a radio wave signal. Magnetic Resonance Imaging allows the delineation of brain images into grey and white matter. The comparison of in vivo MRI scans of healthy volunteers and patient populations is essential for the investigation of normal and abnormal brain development. The separation of grey and white matter is important, since these two tissue-classes are unique and differ in brain diseases. For example: grey matter reduction has been described in schizophrenia and Alzheimer's disease, whereas white matter integrity is an important indicator for normal brain maturation. Grey matter consists of non-myelinated neuronal cell bodies and glia. In contrast, white matter is mostly made up of myelinated axons and axon fibers. T1 and T2 weighted MRI images differentiate between grey and white matter on the basis of image contrast through variation in voxel intensity. Thus, the interface between grey and white matter regions is complex. We used two methods of quantitative analysis in the studies described in chapter 2 and chapter 5 of this thesis. The first method gives total and regional brain (grey + white matter) volumes for each individual study subject by manually tracing regions of interest. The volume of each region is then calculated by multiplying the summed pixel cross-sectional areas by slice thickness. This method is very time consuming and requires good intra- and interrater reliability. The second method we used is called voxel based morphometry (VBM) which uses a simple statistical comparison of grey and white matter partitions following a segmentation algorithm based on the general linear model (GLM). VBM of MRI images involves the following four computational steps:

a) normalizing all MRI images to the same stereo-tactic space, using a template (provided by the Montreal Neurological Institute (MNI)),
b) extracting grey matter, white matter and cerebrospinal fluid (CSF) from the image by segmentation algorithms,
c) smoothing the images with a Gaussian kernel filter and
d) performing a statistical analysis of group differences in grey and white matter and CSF.
The study described in chapter 4 employs functional MRI to investigate neurobiological correlates of social dysfunction in the VCFS population. Functional MRI is a novel neuro-imaging method, relying on the principles of MRI, which allows for non-invasive investigation of brain activity. Functional MRI relies on a naturally occurring contrast agent to visualise variation in blood oxygenation patterns in the brain, elicited by haemodynamic changes. This has led to the in vivo observation of brain activation during behavioural and cognitive tasks. In this study a task of facial emotional processing (previously used in people with autistic disorders) is used as an indirect marker for social cognition.
REFERENCES


