Brain structure and function in velo-cardio-facial syndrome with and without psychosis
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SUMMARY

In chapter 1 velo-cardio-facial syndrome (VCFS), or 22q11 deletion syndrome and its association with psychosis have been described. The rationale of this thesis was formulated: "What can we learn from VCFS on the aetiology and pathogenesis of psychosis and schizophrenia?"

In chapter 2 and chapter 5 structural brain anatomy has been explored in an adult population with VCFS using quantitative (voxel-based morphometry and manual tracing) and qualitative MRI. In chapter 2 a group of adults with VCFS, both psychotic and non-psychotic, are compared with a control group of similar intellectual ability. The results demonstrate that VCFS people had: i) a high prevalence of white matter hyperintensities and abnormalities of septum pellucidum; ii) a significantly smaller volume of cerebellum; iii) widespread differences in white matter bilaterally and regional specific differences in grey matter in left cerebellum, insula, frontal and right temporal lobe. Thus, deletion at chromosome 22q11 appears to be associated with brain abnormalities that are most likely neurodevelopmental and may partially explain the high prevalence of learning disability and psychiatric disorder in VCFS. However the presence of psychosis could have been a confounding factor in this study. Chapter 2a discusses frontal dysmaturity as a possible explanation for the discrepancy between the results that have been described in chapter 2 and those from neuroimaging studies that have been carried out in children with VCFS. In chapter 5 comparisons were made between those subjects with VCFS who had developed psychosis and those who had not. A third, healthy non-psychotic IQ matched control group was used to differentiate which differences were likely to be specific for VCFS and which were likely to be associated with the presence of psychosis. People with VCFS and psychosis, compared to both the controls and non-psychotic VCFS people, had a significant (p<0.05) reduction in volume of whole brain brain matter (white + grey) and whole brain white matter; and an increase in total and sulcal cerebrospinal fluid volume. Both VCFS groups had a reduced cerebellar volume compared to controls. Small cerebellum seems specific for VCFS independent of the development of psychosis. Psychosis in VCFS seems to go together with generalised brain matter loss and particularly affecting white matter, while differences in tissue composition in the psychotic group are concentrated in frontal regions. The results support the hypothesis that psychosis in VCFS is a progressive neurodevelopmental disorder with possibly genetically determined brain dysmaturity. Studies with larger samples are needed to replicate our findings.

In chapter 3 and 6 the cognitive profile in adults with VCFS is described using a comprehensive test battery that is also suitable for people with learning disability. In chapter 3, a group of adults with VCFS, both psychotic and non-psychotic, is compared with a control group of similar intellectual functioning. Compared to controls, adults with VCFS had significant impairments in visuoperceptual ability (Visual Object and Space Perception Battery), problem solving and planning (Tower of London) and abstract and social thinking (Comprehension WAIS-R). Haploinsufficiency of one or more neurodevelopmental genes mapping to
chromosome 22q11 possibly underly the cognitive deficits observed in individuals with VCFS, however the VCFS group included people with and without psychosis therefore no conclusions could be drawn with regard to the impact of psychosis on cognitive function in VCFS. **Chapter 6** subsequently describes the results of a study using the same test battery in a larger, extended group of adults with VCFS. The VCFS group with schizophrenia compared to the VCFS group without schizophrenia performed significantly (p<0.05) worse on tests of: 1) spatial working memory and strategy formation; 2) the Similarities sub-test of the WAIS; 3) visual recognition; 4) and attention. These deficits may reflect differences in the development and function of frontal brain regions, and this might increase the risk of developing schizophrenia in VCFS. Future studies will need to address how haploinsufficiency of genes on chromosome 22q11 might affect cognition and its relation to the development of psychosis.

**Chapter 4** describes the results of a functional magnetic resonance imaging study in eight adults with VCFS and nine age-IQ matched controls using a facial emotional processing paradigm. VCFS subjects, compared to controls had significantly less activation in occipito-temporal brain regions, regions that are normally involved in face perception. Genetically determined developmental abnormalities in pathways involved in early face processing may underlie deficits in social cognition in people with VCFS.