Brain structure and function in velo-cardio-facial syndrome with and without psychosis
van Amelsvoort, T.A.M.J.

Citation for published version (APA):
CHAPTER 7

DISCUSSION
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The VCFS population is an unique population with an identified genetic defect, a characteristic clinical phenotype and a dramatic 20-30 fold increase in the risk of developing psychosis at young adult age (often diagnosed as schizophrenia). As such it provides an interesting neurodevelopmental model to study the biological markers of psychosis. This was the rationale for the studies that have been described in this thesis. The results presented in this thesis provide a first step to some insights in the biological markers of psychosis in VCFS which is also of relevance to psychosis in the general population.

Limitations

Although we used small sample sizes, the studies described in this thesis have demonstrated that in the VCFS population effect sizes can be quite large. Our sample size and the cross-sectional design are limitations of the studies presented in this thesis, but we were still able to detect several significant differences. In addition we carried out multiple statistical comparisons and thereby increased the risk of a type I error (false positive outcomes). Another limitation is the use of a learning disabled (LD) control group. It is not generally agreed as to which is the most appropriate control group to use when studying people with genetically determined neurodevelopmental disorders. All other authors have used normal IQ controls which could explain discrepancies found between our study results and theirs. Disadvantages of using a borderline LD control group include their relative population heterogeneity, including people with genetically and environmentally determined causes of cognitive impairment which we did not detect using our screening techniques, and they are not representative of the healthy population. Advantages of asking them to volunteer as controls include ability to match on IQ (intellectual functioning is related to brain volume\(^1\)), and to attempt to control for clinically undetected birth trauma (because people with genetically determined LD also have an increased rate of birth trauma) – which affects brain anatomy and cognitive function\(^4\). Ideally we should have had another normal IQ control group in addition to the learning disabled control group. Another limitation is that we did not control for effects of neuroleptic medication: we cannot exclude this as a potential confound in all studies described in this thesis.

Brain anatomy

The results from the neuroimaging data of this thesis emphasize the need to increase our understanding of grey / white matter tissue development in VCFS and how this is affected by psychosis. Ideally, post-mortem neuroanatomical and neurohistological studies should be performed in order to understand the relation between alteration of white and grey matter compartments: are both compartments separately affected? Is the alteration of the axonal tracks responsible or resulting from abnormal neuronal arborization? What proportion of neuroanatomical changes can be attributed to vascular abnormalities? Is polymicrogyria associated with VCFS secondary to vascular abnormalities or due to another developmental abnormality?
The results of our two structural MRI studies suggest that white matter is more compromised than grey matter in VCFS\(^*\) and maybe even more so in psychosis associated with VCFS\(^*\). Also, our results suggest that volume of total and peripheral CSF is increased without enlarged ventricle size in psychosis in VCFS. These findings are in contrast to findings of schizophrenia in the general population the most consistent one being enlarged lateral ventricles\(^*\). Also grey matter reductions have been reported more frequently in schizophrenia than white matter abnormalities in schizophrenia in the general population. However, schizophrenia is increasingly seen by some as a supraregional disorder involving interconnecting white matter tracts\(^*\), and studies using newer neuroimaging techniques such as diffusion tensor imaging do report abnormalities of white matter structure. Most likely answers to the questions above will require larger and longitudinal MRI studies as well as neurohistological studies on single-gene knock-out animal models to help us understand the contributions of the different genes, as well as secondary expressed genes, related to the commonly 3Mb deleted region in VCFS.

**Brain function**

The results of the studies of brain function as described in this thesis highlight the importance of using an IQ matched control group to control for the effects of low intelligence on the specific tests of cognitive functioning, including attention, memory, executive functioning, and the facial emotional processing task of the fMRI study. This approach enabled the studies to highlight specific areas of difficulty in the adult VCFS population. The neuropsychological data suggest that performance on non-verbal tasks is particularly impaired with relative preservation of verbal and/or memory tasks in adults with VCFS\(^*\). Also, within VCFS the presence of psychosis affects performance on executive tasks in particular with relative sparing of verbal memory tasks\(^*\). This latter finding is in contrast with neuropsychological data from people with non-VCFS associated schizophrenia\(^*\). Our findings suggest a profile that resembles one of a non-verbal learning disability (NVLD). This is in agreement with the VCFS literature of children with VCFS\(^*\). Rourke has suggested that NVLD is a white matter syndrome i.e. that NVLD develops as a result of a primary processing dysfunction associated with early white matter abnormalities in primarily the right hemisphere\(^*\). The characteristic features of NVLD are (1) impairments of bilateral tactile perception, (2) discrimination and recognition of visual detail and visual relationships, (3) bilateral psychomotor co-ordination and (4) problem solving with novel stimuli. Consequently, children with NVLD develop difficulties with visual attention, social competence, emotional distress, concept formation and problem solving. In addition, NVLD children often exhibit initial developmental delays in language development, followed by rapid acquisition of verbal skills. The children develop good cognitive and functional abilities in auditory perception and memory, simple motor tasks and learning of rote material. Problems with social perception, judgement and interactive skills are also reported in children with NVLD\(^*\). In our structural neuroimaging studies widespread white matter abnormalities were observed and our cognitive data highlight similar problem areas as those seen in people with NVLD. Also, it could explain our findings from our functional MRI
study: aberrant development of cortico-cortical networks including (white matter) pathways between the visual and somatosensory cortices may partially underlie problems in social functioning in VCFS

Candidate genes
There are several potential candidate genes located on chromosome 22q11 that could theoretically be involved in the aetiology of psychiatric disorders that are associated with VCFS. They could be involved in neurotransmission (Catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH)), in vascularisation (TBX1), or neural crest development (Ubiquitin Fusion Degradation 1 like (UFD1L)). However, investigation of the potential contribution of these individual candidate genes is still in an early phase. It is unlikely that just one or two genes will be responsible for the psychiatric and cognitive-behavioural phenotype associated with VCFS. The currently best studied candidate gene of the 22q11 region is the COMT gene. Activity of this enzyme that is involved in catecholamine inactivation, is governed by a single nucleotide polymorphism resulting in 3-4 times difference in COMT activity. Moreover, the high activity (Val) allele, (because it increases prefrontal dopamine catabolism) impairs prefrontal cognitive function, and slightly increases the risk for schizophrenia. The low activity (Met) allele has been associated with aggressive behaviour in schizophrenia. COMT seems to have specific affinity for frontal brain regions and accounts for variation of prefrontal cortex-related cognitive abilities in human populations. Dysfunction of, or abnormal connectivity to frontal brain regions most likely underlie at least partially the cognitive, behavioural and psychiatric phenotype that we see in people with VCFS. Because people with VCFS have a reduced gene dosage of COMT, they might be more susceptible for changes in COMT activity, which could affect the integrity of the dopaminergic system, including it’s prefrontal projections and so modulate the risk for the development of psychotic symptoms, anxiety, and externalizing behaviour, and prefrontal cognitive dysfunction.

Future research
Ultimately, understanding how specific genes impact on brain development and neuronal function will help us to better understand the specific cognitive and psychiatric profile associated with VCFS, and allow us to better address the needs of affected individuals and their family. VCFS is a model system for examining the multifaceted nature of behavioral development that will give us insight into pathways leading to psychosis, particularly schizophrenia. Methodological approaches, developed to study neurogenetic disorders like VCFS, will set a path and make tools available for the investigation of future candidate gene(s) of symptom dimensions of schizophrenia, mood disorders or ADHD. Future research focussing on relating genetic variables with neuroimaging, clinical, neurophysiological and neuropsychological outcome measures in VCFS will help us to increase our understanding of the neurobiology of these psychiatric disorders.
REFERENCES