

The Brain and VCFS – What We Know

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Over the last twenty years, brain research interest in VCFS has escalated rapidly. This increase is primarily due to two reports published in the early 90's. One documented the discovery of the deletion on chromosome 22q11.2 by Pete Scambler and colleagues, and the other one was by Bob Shprintzen and his colleagues which indicated that the risk of mental health problems might be increased among people with VCFS. Concurrently, better access to non-invasive magnetic resonance imaging (MRI) and the rapid development of faster and more accurate ways of analysing and interpreting the structural and functional properties of the brain have led to an "explosion" in the field of neuroscience.

Increased knowledge of how the deletion influences the structure and function of the brain may explain why people with VCFS have specific behavioural problems or disorders. This can help determine better targeted interventions. It may also help clinicians predict if some people are at an increased risk of specific disorders. Although the research on brain structure and function is progressing and becoming increasingly sophisticated, it is important to remember that it is NOT yet possible for a clinician to look at the brain of an individual with VCFS and predict individual outcomes. What we can say is how the brains of people with VCFS, as a group, generally differ from typically developing people.

The earliest studies of brain anatomy involved clinical observations of structural brain features: that is, trained clinicians looked at images of the brain and determined if they could see lesions or structural differences in the size and shape of the brain.

This method was subjective and limited to detecting gross structural anomalies. However, some consistent findings were reported. Individuals with VCFS are more likely to have:

- Cavum septum pellucidum, which is a cavity between the membranes that separate the lateral ventricles of the brain.
- White matter hyper-intensities, which are very bright spots on MRI images of the brain. The clinical implications of both cavum septum pellucidum and white matter hyper-intensities in VCFS are as yet unknown. Larger lateral ventricles, which are the fluid filled cavities in the middle of the brain. There have been links between mental health disorders such as psychosis and enlarged lateral ventricles, but the individual differences are large and no conclusive evidence exists.
- Reduced vermis, part of the cerebellum. The vermis has been implicated in social cognition.
- Arnold Chiari (or Chiari II) malformations, a malformation of the cerebellum that can result in physical symptoms such as feeding/swallowing difficulties, dizziness and headaches.
- Polymicrogyria, which is the presence of unusually small and numerous folds on the surface of the brain. It happens very early on in development and can happen on one or both sides of the brain. The effects can be very mild and sometimes not noticeable at all, but in more severe cases, can be associated with epilepsy and intellectual disability.

Today new methodologies allow us to measure subtle structural differences that cannot be seen with the naked eye, and to compare the brain anatomy of groups of people with and without the 22q11.2 deletion. Further, by looking at the images of brains from the same individuals over time it is possible to see how the brain develops as people grow older.

It is well established that brains of people with VCFS are affected by the deletion at chromosome 22q11.2 in various subtle ways. In particular, it has been found that people with VCFS have smaller brain volumes throughout the cortical and subcortical regions of the brain. The cortex is the outer surface of the brain, containing grey matter (including neurons), where most information processing occurs. The subcortical area is under the cortex: it contains the inner, non-surface regions of the brain. Both cortical and subcortical regions of the brain are affected in VCFS.

In VCFS, cortical regions in the back of the brain are more affected than the frontal regions. Affected regions include:

- Cerebellum: involved in motor movements but also cognitive functions such as attention, language and emotion processing
- Parietal and occipital lobes: in particular the parietal lobe is a brain region critically involved in integrating sensory information from the different parts of the body but it is also involved in numeracy and visual-spatial processing, so often impaired in VCFS. Differences in these areas may explain some of the cognitive impairments often seen in people with VCFS.
- Fusiform gyrus (a part of the temporal cortex), which is important for face and body recognition and for the processing of facial emotions. Therefore, the fusiform gyrus may be involved in some of the social problems often attributed to people with VCFS.

Changes in subcortical regions of the brain have also been revealed in VCFS. They include:

- Reductions in the hippocampus, which is involved in the formation of memory.

- Enlargement of the striatal structures such as the caudate nucleus. The striatum has been found to be implicated in behavioural problems such as ADHD in people without the deletion.
- Enlargement of the amygdala, which is involved in emotion processing.

Functions of the brain can also be explored using functional MRI (fMRI). With fMRI, it is now possible to get a better understanding of the location and degree of brain activity when a person is carrying out tasks such as remembering events, interpreting facial emotions and so on. Not many fMRI studies have been done in researching individuals with VCFS. However, it has been found that people with VCFS do use atypical regions of the brain when processing faces and solving mathematical and memory problems, compared to people without the deletion.

While there are consistent reports of grey matter abnormalities in VCFS, it nevertheless seems as if white matter is more severely affected than grey matter. White matter is the interconnected axons (cabling) of the brain which allows neurons in different part of the brain to communicate. It is so named because it looks white due to the fatty insulation that is covering the axons. It has been found that in many regions of the brain, white matter is significantly reduced in VCFS. However the corpus callosum, a bundle of white matter tracts connecting the left and the right hemisphere (or side) of the brain, is increased in size. This increase in size may be indicative of a delay in the pruning processes of the corpus callosum that occurs in typically developing adolescents.

Another important aspect of brain function is the role of neurotransmitters.

Neurotransmitters are chemicals in the brain that help neurons send messages to other neurons. There are many different types of neurotransmitters. One type that is particularly affected by a deletion at chromosome 22q11.2 is dopamine. This is because the amount of dopamine in the frontal part of the brain is regulated by a gene that is located within the 22q11.2 region. This is the Catechol-O-Methyltransferase gene or the COMT gene for short. There are two different variants (or types) of this gene (Met or Val).

Normally, people have two copies of this gene and they can either have two of the same type (that is Met/Met or Val/Val) or one copy of each type (Val/Met).

However, people with VCFS only have one copy which means that they either have one Met or one Val copy. The combination of variants influences how much dopamine you have in the frontal cortex. The level of dopamine in the frontal cortex affects cognition (such as memory) and is also related to psychiatric disorders such as psychosis. Studies of how a specific variant of this gene affects people with VCFS are not conclusive. Studies with children who have VCFS have found that the Val variant is linked to increased cognitive impairments compared to those who have a Met variant. These impairments include poorer intellectual functioning, executive function and attentional skills as well as higher levels of anxiety. However, other studies that included older individuals with VCFS have found that the Met variant is a risk factor for psychiatric disorders such as attention-deficit hyperactivity, obsessive compulsive disorder, bipolar disorder and also for psychotic symptoms. Scientists are continuing to test the effects of this gene's variants with larger samples of people with VCFS, which will be more definitive.

The atypical brain structure and function in VCFS is not something that can be compared with a brain that has been damaged by trauma, such as an accident. It is likely due to a dynamic developmental change present from before birth that continues through life. Indeed, some studies following young people with VCFS as they grow up have found that their brain development was different when compared to people without the deletion. It is also becoming evident the boys and girls with the syndrome differ in brain development and that factors such as specific genes have an influence on brain development as well.

Finally, it is important to regard our brain as the complicated and dynamic organ that it is. People who have VCFS have constraints on brain development which might differ from 'typical' development. However, what is "typical" development? We are all unique and have unique experiences that will shape us differently. We know that both genes and the environment play essential roles in shaping brain growth and development throughout our lifetime. Even though children born with VCFS may have brains that look different from typically developing brains, these young brains are amazingly 'plastic', and as are increasingly being understood, to some extent as "malleable to outside influences and, through our research, will be better understood in the years to come.