Adolescent Strugglers and Copers:

How cognitive stress and anxiety precipitate or protect psychosis in the developmental brain vulnerabilities of 22q11.2 Deletion Syndrome or Velo Cardio Facial Syndrome (VCFS).

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A day on current research on Velo Cardio Facial Syndrome also known as 22q11.2 Deletion Syndrome (DS) was held at the Children's Hospital in November 2013, with guest speakers Honey Heussler, Developmental Paediatrician, Mater Children's Hospital, Queensland, Linda Campbell Lecturer in the School of Psychology at University of Newcastle, and Tony Simon a professor of paediatric cognitive neuroscience from University of California, Davis, co-hosted with the VCFS Society.

The rate of adult onset schizophrenia or psychosis in 22q11.2DS is 25-30% (a 30 times increased rate and a similar risk to being an identical twin of someone with schizophrenia). Accordingly, cognitive neuroscientists, psychiatrists and researchers are focused on the behavioural phenotype of 22q11.2DS and funded to research 22q11.2DS as the key to unlock the mechanism underlying risk and protective factors for psychosis in the general population. There are many other significant features of 22q11.2DS: a genetic deletion found in 1/2-4000 live births. These children are at risk of a range of midline abnormalities including heart defects, cleft palate, facial dysmorphism, autoimmune disorders and anomalous brain development.

Heussler gave an excellent review of the biological and medical concomitants. Campbell presented on her extensive survey of parents' experience of service provision compared with Down Syndrome and the lack of multidisciplinary multiagency collaboration, which needs to be continued from childhood to adulthood. An Australian Paediatric Surveillance Unit Study is planned to increase clinician awareness of the needs of young people with 22q11.2DS.

Young people with 22q11.2DS are also at risk of ADHD (50% in preteens and 20% in teens) Anxiety (50-60%) and ASD (20-50%). They have learning problems: IQ 70-85 (+/- 15), verbal domains better than non-verbal, receptive better than expressive. Reading and spelling skills are of low average ability but comprehension is poor; rote memory is strong but complex verbal, spatial and working memory is poor. Attention and executive function are impaired.

European Child and Adolescent Psychiatry Dublin Conference held a workshop on some of the longitudinal cohorts of 22q11.2DS, July 2013. Stephan Eliez from Geneva described changes in cortical thickening seen in sequential MRI brain scans: we all have a reduction of cortical thickening in adolescence, which enhances cognitive efficiency (a pruning process) but 22q11.2DS starts with increased thickness and less gyrification or cortical folding and then has excessive and continued loss of thickening beyond controls. In those with ASD and Schizophrenia this effect is greatest in the limbic system or emotional brain; in those with ASD it is more in the superior temporal sulcus and amygdala, for those who develop schizophrenia it is more in the superior temporal gyrus and the anterior cingulate gyrus.

Further, functional MRI scans that record co-occuring activity enable maps of functional connectivity. These show disconnectivity of the anterior cingulate lobe, the superior temporal lobe and the superior parietal lobe. By looking at the vector patterns of disconnectivity he is able to predict which have schizophrenia with 88% accuracy. Stress and excess cortisol activity also increase cortical thinning.

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Many present with psychotic symptoms, some recover and some progress to psychotic illness. Stress management is important for these early presenters, but some drugs are known to reduce cortical thinning especially of the anterior cingulate, including valproate, SSRIs, and possibly Omega 3 in fish oils. Those with hyperactivity are more affected with cortical thinning in the caudate nucleus and fronto striatal pathways. Jacob Vorstman's 22q11.2DS cohort from Utrecht showed at 13 years of age 25% had psychotic symptoms and 8% had psychotic disorder but by 18 years there were 30% with psychotic symptoms and 30% with psychotic disorder. Conversely 64% of those with psychotic symptoms at 13 had remitted by 18. He postulated that stress factors affected those that recovered or deteriorated. His younger cohort followed from 5 to 10 years show a relative cognitive decline from an average IQ of 79 to 69, with a

greater decline in verbal skills than performance skills.

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These genetic phenotype changes in cortical development and IQ over time set the scene for Tony Simon's research: Simon observed that there is great variation across children and across ages despite the 22q11.2DS limitations in competence in numerous domains. Some performed better than testing predicted and others fell short. Screening with the BASC II (Behavior Assessment System for Children), 'Copers' showed lower anxiety and higher real world functioning and 'Strugglers' show the reverse, with higher anxiety and poorer adaptive functioning. He has shown that parent reported Anxiety levels from separation anxiety, physical injury fears, panic, agoraphobia, OCD were related to adaptive functioning, but not social phobia or Generalised Anxiety Disorder on the Spence Child Anxiety Scale. Whereas typically developing children show a reduction of separation anxiety with age, in 22q11.2DS separation anxiety increases in age in some, more anxious, children.

Longitudinal data shows a complex interaction of developmental delay and "sheltering" but after the age of 9 there are divergent trajectories between 'Copers' and 'Strugglers', whereby the 'Copers' have a decline in anxiety and the Strugglers show an increase. His hypothesis is that 'Strugglers' have an excess 'allostatic load', ie in trying to keep up with their educational and social challenges, they induce a stress diathesis which causes significant wear and tear on brain development and function. In keeping with this, it is found that adaptive functioning in 22q11.2DS is not predicted by IQ but by anxiety levels (Angkustsiri *et al* 2013).

Simon shows that on immediate attention perceptual tasks young people with 22q11.2DS show less accuracy on visual and auditory response eg to picking the shorter of two stimuli, (but not in the pitch) suggesting they have greater problems on selection and filtering of visual and spatial attention tasks. He has then compared attentional patterns for faces with neutral, positive and negative affect. Typically developing kids show a 'relative positive emotion bias' in their attentional style (spending more time unconsciously looking at happy faces), whereas those with 22q11.2DS show a 'relative negative emotion bias' (for angry or neutral faces). This difference for a relative positive or negative emotion bias was also related to the anxiety/adaptive function levels. This attentional bias to affect also correlates to whether they are 'Copers' or 'Strugglers' in terms of their levels of anxiety.

On an Autistic Diagnostic Interview (Revised) 40-50% were considered to have ASD from parental report. Similarly, Angkustsiri *et al* also found in a sample of 29 cases of children with 22q11.2DS, high ASD scores in 7 cases on the Social Communication Questionnaire or an Autistic Diagnostic Observation Schedule, but none of the cases were diagnosed ASD on strict criteria. This discrepancy was explained by the negative affect gaze avoidance. Shapiro (2013) found that inhibitory responses (on Go No Go tasks) also got worse in older teens with 22q11.2DS.
Deng looked at Anxiety and ADHD in 22q11.2DS and found a huge overlap: of 79 cases, 73% had anxiety, 51% had ADHD and 42% had both, while only 18% had neither. Beaton showed that children with 22q11.2DS had higher rates of depressive symptoms on the Childhood Depression Inventory and higher salivary cortisol levels (the stress hormone) both before and after a stress test (a mock MRI procedure).

So if an IQ of 75 means operating as a 9 year old in a 12 year old's world for a young person with 22q11.2DS, it is likely that this contributes to 50-60% having significant anxiety, and 20-50% having ADHD, mostly inattentive or combined type. Can the hyper-arousal/hyper-vigilance from anxiety present as ADHD? Does the mismatch in cognitive and social demands result in anxiety and avoidance leading to frequent ASD diagnoses? Could reducing the 'allostatic load' protect against psychosis?

Gothelf and colleagues (2013) found in 22q11.2DS that having an anxiety disorder as a child was predictive of psychosis. Of 10 who developed psychosis, 9 were diagnosed with an anxiety disorder at baseline. Tang and colleagues (2013) also found those with isolated psychotic symptoms, such as 'sees things that are not there', 'has strange ideas', 'hears sounds that are not there', or 'seems out of touch with reality' were more likely to have a mood or anxiety disorder. Yet 90% have one prodromal feature of psychosis which does not predict which will develop psychosis later, rather it is those with high anxiety that are at greater risk. The gene for Catechol-O-methyltransferase (COMT) is part of the 22q11.2 deletion and one of several enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine. The genetic variance of COMT in

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22q11.2DS causing lower activity may be another part of the process associated with cognitive decline in adolescence.

Accordingly, we are able to identify a group of 22q11.2DS who are psychosis prone, by measures of declining cognitive capacities, high anxiety, and relatively low adaptive behaviour skills. Could cognitive impairment lead to stress and chronic stress lead to anxiety, depression and low self-esteem, and the affective avoidance lead to further slowing of development with increased cortical thinning and loss of connectivity between different cerebral areas and functions? Their group now provides 2 days intensive assessment to identify the family, school, community, cognitive and psychological factors to determine a ‘Coper’ or a ‘Struggler’ trajectory. They then intervene to reduce the ‘allostatic load’ thereby reducing stress and anxiety through changing the child, family and school environments. For the child they use cognitive training, behavioural and CBT and SSRIs. For the school they develop individual educational plans and careful calibration of challenge based on testing. For the family they provide coping strategies for parents, matching parent/child expectations.

This package of assessment and intervention is being subjected to further evaluation, but anecdotally they feel confident that their intervention does change the young people with 22q11.2DS from ‘Strugglers’ to ‘Copers’ and those who look like they were going to develop a schizophrenic psychosis appear to change. Tony Simon believes that intervention really is reducing the statistics on the number of young people with VCSF developing psychosis.

These principles of ‘allostatic load’ and ‘Struggler’ vs ‘Coper’ status are not specific to 22q11.2DS but could apply to many with intellectual disability and emotional behavioural problems, and also those with early psychosis presentations. The concept of ‘Struggler’ vs ‘Coper’ is used in many situations in severe disabling psychiatric disorder, such as somatoform disorders and is frequently central to improved outcome. Tony Simon has developed a metric of cognitive and affective struggling in the context of the behavioural phenotype of 22q11.2DS. This model also seems to link to stress processes and influences on brain development. It may be the genotype that specifies what part of the brain development is most affected. Establishing an evidence base to such a concept may have wide implications to helping young people with the most disabling mental health conditions. Yet again, a behavioural phenotype is able to provide evidence of brain and psychological processes which may have significance for broader clinical practice.

References

Angkustsiri, K. et al. (2012). An examination of the relationship of anxiety and intelligence to adaptive functioning in children with chromosome 22q11.2 deletion syndrome. *Journal of Developmental Behavioural Pediatrics*. Vol 33, Pp. 713–720.

Campbell, L. (Accessed 2014). http://www.vcfsfa.org.au/media/Linda%20Campbell%202011.pdf

Simon, T. (Accessed 2014). http://www.ucdmc.ucdavis.edu/mindinstitute/research/cabil/cabil_projects.html

Eliez, S. (Accessed 2014). http://www.vcfsef.org/Resource_image/939Psychiatric_Problems_Adolescence_VCFS_Eliez-2013.pdf
Vorstman, J. (2013). Conference Presentation: ESCAP.

Shapiro, H., *et al*. (2013). A cross-sectional analysis of the development of response inhibition in children with Chromosome 22q11.2 Deletion Syndrome. Frontiers in Child and Neurodevelopmental Psychiatry. Vol 4, Pp. 81.

Gothelf, D. and Eliez, S. *et al*. (2013). COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome . Nature Neuroscience. November Edition.

Gothelf, D. *et al*. (2013). Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: a longitudinal 2 site study. Journal of the American Academy of Child and Adolescent Psychiatry. Vol 52, Pp. 1192-1203. E3.

Tang, S.X. et al. (2013). Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. Psychological Medicine. Vol 1-11. doi:10.1017/S0033291713001669

Deng. Unpublished thesis.

Beaton, E.A. and Simon, T.J. (2011). How might stress contribute to increased risk for schizophrenia in children with chromosome 22q11.2 deletion syndrome? Journal of Neurodevelopmental Disorders. Vol 3, Pp. 68-75. http://www.vcfsef.org/Resource_image/Elliott%20Beaton%20VCFS_2010_Talk_Children%20with%20VCFS%20report%20higher%20levels%20of%20anxiety.pdf