a note from David Dossetor...

Behavioural Phenotypes: A Window into the Mechanisms of the Mind

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The emotional and behavioural problems of young people with intellectual disabilities have regularly been overlooked as just part of their intellectual disability, what has been termed 'diagnostic overshadowing'. Not only is recognising and treating their psychological and social maladaptive problems of critical importance to their wellbeing and quality of life, but understanding these problems provides light on the processes of the early development and mechanisms of the mind. Amongst the causes of disability are genetic conditions and many of these genetic conditions have characteristic patterns of behaviours. Particularly as we are able to discover and define genetic abnormalities, so we are able to illustrate that certain genes or their problems are biologically linked to specific behaviours.

Behavioural phenotypes are defined as characteristic motor, cognitive, linguistic and social abnormalities which may or may not constitute a psychiatric disorder which are consistently associated with a biological disorder (Flint, 1996). It may apply to syndromes where a genetic aetiology has not been defined. The term was coined by William Nyhan in 1964, from the Greek word Phainein- to show. A list of some of the best known behavioural phenotypes is listed on page 5*.

In most instances the manifestations of the mind are seen as unrelated to the functioning of the brain, what Descartes call dualism. At some level most people accept that conscious processes have a biological basis. Genetic conditions with specific behavioural phenotypes provide the best models for examining and understanding the biological basis of mental function and behaviour.

There are approximately 7,50 known genetic abnormalities, and in my clinical practice I come across 2-3 new genetic conditions a year and many have characteristic behavioural phenotypes. Each condition gives clinical researchers an opportunity to look at what underlies certain behaviours by finding differences of brain structure and functional processes associations with that genetic abnormality. With the genetic revolution of the last decade the science is developing rapidly, even though it is based in most cases on fairly rare conditions or populations of children and adults. For example Copy Number Variants (CNVs) are repeater sequences in the human genome which can now be detected by DNA chips, which are identifying a whole new lot of genetic disorders. One paper last year reported on 22 new such conditions (Viseer et al, J Med Genetic 47, 2010). Both 7% of Autism and of Schizophrenia are associated with CNVs.

The Society for the Study of Behavioural Phenotypes is a small international multidisciplinary group of clinicians and researchers that meet every year. Last October I attended the annual meeting in Pavia, a renaissance town 30km south of Milan, that, in its heyday, boasted 100 brick towers as a sign of affluence. The Meeting was held in the beautiful old library of the 800 year old University and Medical School. It was in Pavia that Camille Golgi in 1875 developed the Golgi silver nitrate stain which first enabled the visualisation of brain neurones and dendrites, the connections between cells. We saw his Nobel Prize, awarded in 1906 for this achievement, and his original ink drawings of neurones. James Harris, Professor of Psychiatry and Paediatrics at Johns Hopkins, Baltimore, confirmed the importance of his achievement as, even with today's technology, his stain is still the best way of viewing whole neurones, and abnormalities of dendritic structure and connectivity is now the most common biological association of intellectual disability, whether this is Downs Syndrome, Fragile X, Neurofibromatosis 1, Tuberose Sclerosis, Williams Syndrome, Phenylketonuria or Lesch Nyhan Syndrome. For example Lesch Nyhan Syndrome, which is manifest by over production of Uric acid, intellectual disability, movement disorders and self injurious behaviour (SIB) including chewing of lips and fingers, has a reduction of presynaptic dopamine transfer with reduced long dendrites and dendritic spines. There is also reduction of caudate nucleus volume and the hypoxanthine-guanine phosphoribosyltransferase (gene missing, necessary for production of generation of purine nucleotides and adenosine-5'-triphosphate (ATP), a multifunctional nucleotide which stores energy in cells. This is one example how a behavioural phenotype can lead to understanding structure and function of the brain.

Chris Oliver Professor of Psychology of the Cerebra Centre, Birmingham University UK, has used behavioural phenotypes to illustrate different levels of structure and function that influence behaviour. He expanded the causal traditonal framework of behaviour of impairments, disabilities and handicaps to;

i) **The physical phenotype** (Impairments) Including: genetics, intracellular chemistry, cellular connectivity and functionality, connections between different regions of the brain, and physical health,

ii) **The cognitive endophenotype** (Disabilities) Including cognitive capacity, communication skills, neuropsychology, theory of mind, executive function skills, patterns of behaviour eg of attention and gesture, and

iii) **The behavioural phenotypes** (Handicaps with environmental interaction) Including the quality and match of environment, the influence of services systems and the wider political, economic and policy environment in which services and the individuals they serve exist.

Oliver and other speakers then illustrated this with findings from behavioural phenotypes. Cornelia de Lange's Syndrome (CdL) suffers extreme SIB. This behavioural phenotype illustrates the problem of understanding pain in the absence of a capacity to explain. 80% suffer gastro oesophageal reflux and treatment with omiprazole which reduces the effects of the gastric acid helps in many cases. Other SIB can be related to middle ear disease found in 94% and hearing loss found in 80%, ophthalmology problems

with ptosis, myopia and retinal detachment or dental problems, leading to head bashing, and dropping on to their knees with Perthes's Disease of the hip, along with other orthopaedic problems. 25% also have renal problems with vesical ureteric reflux, and renal function decline. This behavioural phenotype illustrates the importance of searching for the unseen medical problem in those with limited communication problems. It is evident that this can apply in any case of someone with

The psychiatry of intellectual disability is exciting and novel and it has potential to influence our understanding of the mechanisms of the mind in special populations

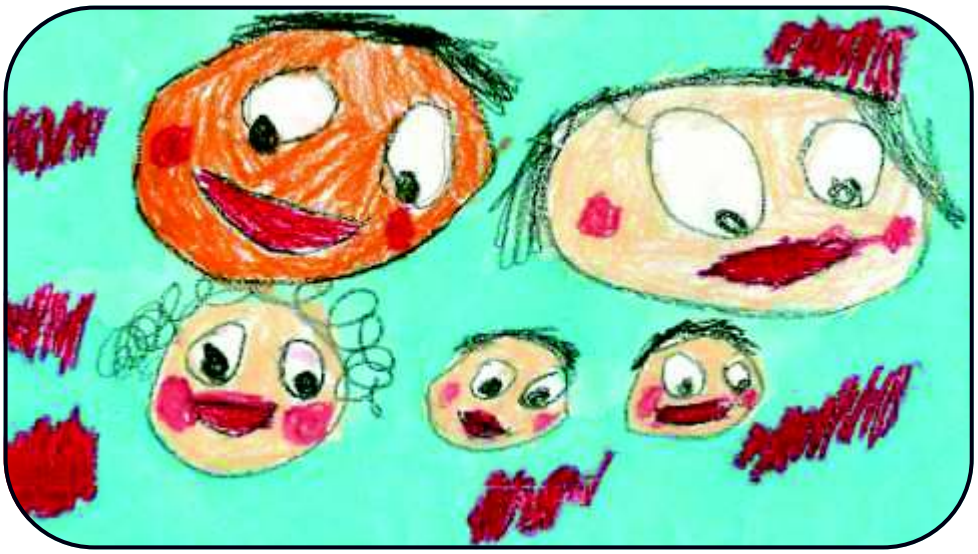
distress and limited communication, yet there is a real paucity of the empirical literature on the effects of physical ill health on behavioural problems. One report quoted that 50% of children with Autism had gastro oesophageal reflux.

There is a mild version of CdL now recognised on a scale score of symptoms. They usually have greater problems of expressive language, often with no verbal skills, yet can even be of normal intelligence. 40% of CdL show features of selective mutism. If asked a question they show increased fidgeting. Is this a factor in the increase in impulsivity and hyperactivity with increased age? They also show increasing social emotional problems or Autistic Spectrum Disorders (ASD) (30%) with time although they have less stereotypic features and more social and communication features on the ADOS (Autistic Diagnostic Observation Schedule). Those with CdL also use more gestures than other groups in terms of gestures per 100 words and Chris Oliver illustrated the differences in gestural communication which they use, and how the gesture of self revealing palms is absent when theory of mind is missing. It is suggested that problems with communication leads to anxiety that leads to challenging behaviour. We were exposed to a lovely demonstration of Augmentative and Alternative Communication (AAC) using reading to enable the development of communication and a decline of SIB.

CdL has several genes identified, the main one is found in 50% of cases and is called NIBPL (deletion of chromosome 5p13.2). The theory is that the various genes are involved in the expression of Cohesin which is an enhancer for various genes and involved in linking chromatids in mitosis and involved in many tissues and the linking of cells together as illustrated in the characteristic problems of limb, bone and nerve growth. Synaptic development goes through growth, pruning and maintenance. It is the pruning at 4 years of age that doesn't occur in CdL leading to ID and ASD features. This too is a model of how pruning of neurones and dentrites may provide a model for understanding other cases of ASD and ID.

Jo Moss has looked at the patterns of repetitive/stereotypic behaviour using the Geddes Compulsive Behaviour Checklist across various syndromes. This demonstrates that although many different syndromes have significant autistic features, there are discrete and definite differences which are recognisably part of the syndrome characteristics, but what specific implications do they carry? CdL show increased ordering, completeness, cleaning, checking and grooming than expected for ASD. Smith Magenis Syndrome have repetitive behaviours/obsessions about people, familiar or strangers (as well as extreme impulsiveness). In particular, Prader Willi has a characteristic pattern of increased repetition of questioning, routine and hoarding. The adherence to routine is related to problems they have with attention shifting and visuo-spatial tests, which when stressed, increases anxiety, and risk of aggression. Oliver's team have shown that Functional Magnetic Resonance imaging in Prader Willi has increased frontal activity in attentional shift, whereas as in the controls it is more parietal, suggesting that in Prader Willi when attentional shift capacity is tested, they need to use a compensatory mechanism in the frontal lobes which reduces their cognitive reserves. This was illustrated with a card sorting test where if the rules of sorting are increased to more than one category, they make greater mistakes and get angry. This problem was associated with increased scores on the 'Brief', a measure of Executive Function, compared for example with Downs Syndrome. Similarly, those allowed to develop greater routines are more aggressive with change. This neuropsychological observation can lead to behavioural vulnerability in transition eg from school to post school options. An intervention using a visual/card warning of change of routine has been helpful to reduce levels of aggression. How often do we think about the problems of attention shift might lie behind resistance to change or aggression?

How Autism has a negative effect on family interaction and attachment is well described. Angelman's Syndrome (the happy puppet syndrome, chromosome 15 q11-q13) illustrates the opposite behaviour/environment interaction: Those with Angelman's have increased sociability, classically described as having "a happy disposition with inappropriate outbursts of laughter". It is observed that they are more likely to initiate social contact and this has an effect making the carer smile and keep on smiling! Thus illustrating an effect of a gene acting on the relationship environment, leading to a mutual positive affect.



Terje Naerland from Norway proposed an interesting psychological phenomenon in ASD. He identified 'focus related performance problems" in 10% of ASD and 50% of Down's Syndrome with autism and Tuberose Sclerosis with autism. If a carer draws attention to their performance of an action it inhibits them and can even lead to the loss of skills. They learn by incidental learning such as copying others. Performance is smooth if unobserved but they stop if observed. So many interventions routinely used are by design at risk of impairing performance or compliance because they focus on the desired behaviour such as through the use of over-learning, use of praise and even the use of token economies. This highlights that no approach is universally good for everybody; even showering rewards and social approval can be harmful.

The study of behavioural phenotypes is also leading to innovation in medical treatments. Some remain experimental such as the use of deep brain stimulation by electrode implantation in Lesch Nynhan Syndrome. James Harris described how deep brain stimulation through the introduction of electrodes precisely into the basal ganglia of the brain was ethically approved to improve dystonia but was also found to reduce SIB incidentally. The study was able to show, using proton magnetic resonance spectroscopy, basal ganglia dopamine neurotransmitter deficits of 60% in putamen and caudate, and the electrical brain stimulation increased dopamine action in meso cortical and frontal lobe neuronal projections. There is some suggestion that in the mainstream population low basal ganglia dopamine levels is associated with emotional dysregulation.

Petrus de Vries, a child psychiatrist from Cambridge has studied the neuropsychology of attention in the Tuberose Sclerosis Complex (TSC). He found that even adults of normal intelligence with TSC have specific problems in dual tasking, for example when visual selective and auditory sustained attention tasks were combined in a cross-modal dual task. His work has drawn attention to a developmental sequence of attentional skills, and the importance of neuromolecular protein TSC1-2 protein which affects higher cognitive functioning separate to functional deficits from the anatomical changes of TSC tubers in the brain. Rapamycin is an immunosuppressant medication used in transplantation, eg of kidneys, to reduce the risk organ rejection. In animal models of TSC Rapamycin has been found to shrink tumours and improve memory, possibly through effects on the hippocampus where changes in electrical activity are found, reducing the long term potentiation. Thus Rapamycin is being explored in human trials and is reducing levels of an abnormal neuroprotein 'mTOR' (target of rapamycin), improving cognitive functioning and even causing TSC tubers and tumours to shrink.

Possibly the development of greatest impact and controversy is the mGlu 5 antagonist trials in Fragile X led by Randi Hagerman at UC Davis Medical Centre, Boston. Fragile X which is the most common cause of intellectual disability and autism is due to an increase in trinucleotide CGG repeats in the X chromosome. In most healthy individuals, the number of nucleic acid CGG repeats are fewer than 40. When the repeats are over 200, this causes methylation and deactivation of the FMR1 (fragile X mental retardation 1) gene which codes for the fragile X mental retardation protein (FMRP) and FMRP is thought to downgrade the development of synaptic connections between nerve cells in the brain and cell-to-cell synaptic communication. The synaptic connections between nerve cells change and adapt over time in response to experience which is important for learning and memory. Without adequate FMRP, an RNA-binding protein, severe learning deficits or mental retardation can develop, along with physical phenotypic abnormalities seen in fragile X syndrome. The functions of FMRP in different domains is still relatively unknown. One hypothesis is that many symptoms are caused by unchecked activation of mGluR5, a metabotropic glutamate receptor, which was found in a 2007 mouse model study to contribute significantly to the pathogenesis of the disease; suggesting that mGluR5 blockers could be used to treat fragile X syndrome.

There are a number of mGluR5 blockers drugs available including lithium, used in bipolar disorder, Minocyline, an antibiotic, an experimental drug STX107 and Baclofen, used for relaxing muscle tone. There is particular interest in the racemic form of Baclofen, Arbaclofen, which is 10 times more effective than the levo form, that is the right handed version of the molecule, versus the mirror image or left handed version. Hagerman has found 70% improvements including in sociability in a randomised controlled trial of Fragile X. There are delays in the release of this treatment due to a drug patent legal battle on whether the racemic molecule constitutes a novel drug. Similar effects are also reported in a proportion of people with autism. It can't be long before specific Fragile X treatment clinics start up!

This brief conference report illustrates how exciting and novel the psychiatry of intellectual disability is, and how it has potential to influence our understanding of the mechanisms of the mind in special populations and I suspect in mainstream populations. If this introduction interests you, or you have observations on behavioural phenotypes that you would like to share, then please make sure you join us at this years meeting of the Society of the Study of Behavioural Phenotypes, which is to be held in Brisbane 5-7th October 2011 hosted by Dr Honey Heussler; further details at: www.ssbp.co.uk/ssbp.

Relevant Reading:

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Flint J. 1996. Annotation: Behavioural Phenotypes: a window onto the biology of behaviour. Journal of Child Psychology and Psychiatry 37(4):355-367.

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**Best Known Behavioural Phenotypes*

Fragile X
Most common form of inherited ID, responsible for 30% X-linked ID. Fragile site @ Xq27.3 The number of CGG nucleotide repeater sequences and more than 320 is proportional to the level of intellectual disability. ADHD in 75%; PDD like symptoms; self injurious behaviour biting hand; picking skin when excited; hand flapping; Communication problems.

Prader Willi

Characteristic physical appearance, extreme overeating & obesity, short stature, hypogonadism, mild ID(IQ 30-85), skin picking, obsessive behaviours, temper tantrums, sleep abnormalities. 1/10,000. Deletion in paternal chr 15q11-13, or maternal disomy or translocation or mutation of an imprinting centre (<5%). Previous reports of increased rates of affective or bipolar psychoses.

The rarer genetic cause of Prader Willi Syndrome, of maternal uniparental disomy of chromosome 15 in adults suggests it may be the highest risk of schizophrenia in any population (Dykens, 2001).

Velo Cardio Facial Syndrome

Deletion of 22q11, characteristic dysmorphology, cleft lip and or palate, learning disability,

Behaviour in childhood: Simple Phobia 22.6% Anxiety Disorders 17% Eneuresis 14% Major Depression 12% & Others. Psychiatric disorder found in adult populations to have a prevalence of :- 42% major psychiatric disorder, including 30% psychosis, and 24% schizophrenia, (with stronger positive symptoms and weaker negative symptoms than is normally seen)

Smith Magenis Syndrome
Deletion of chromosome 17p11.2, 1/25,000. Short, characteristic facies, neurological features etc.

Intellectual Disability, ADHD 90%, aggression, autism, self injurious behaviour, inverted sleep and circadian melatonin cycle, obsessions, anxiety, specific learning problems, self hugging etc

Tuberous Sclerosis
Autosomal Dominant, triad of adenoma sebaceum, fits and Intellectual Disability (less than 30% have classic triad) (38% have average IQ); with hyperactivity & social impairment. TS Complex as involves all tissues; 80% have fits. 70% have behaviour disturbances incl: 36% autism, asperger's, and social impairment; many have infantile spasm assoc. 35% ADHD, 35% obsessive/ritualistic behaviour. 60% sleep problems, 1/3 Self injurious behaviour.
2 groups: tubers in temporal lobe associated with ASD, intellectual disability related to total mass of brain tubers.

Cornelia de Langes Syndrome
Characteristic appearance, short, abnormal growth eg of limbs, self injurious behaviour.

Angelman's Syndrome, the happy puppet syndrome
Deletion of same part of chr. 15q11-13 as Prader Willi but from maternal gene.

Sotos Syndrome or Cerebral Gigantism

Syndrome specific symptoms and signs
Hyperphagia of Prader Willi, "Cry of the cat" of 5p Syndrome and Self-hugging in Smith Magenis Syndrome (Dykens, 2001).

Symptoms over representated in syndromes
Some symptoms are over-represented in several conditions such as: -

- Overactivity and inattention seen in Fragile X and William's Syndrome
- Self injurious behaviour is seen in different syndromes: -
- Extreme lip and finger biting in Lesch Nyhan Syndrome. The specificity of SIB in Lesch Nyhan Syndrome raises the suspicion of abnormalities of purine or dopamine function in this pattern of SIB.
- Hand biting in Fragile X
- Skin picking in Prader Willi Syndrome.
- Head banging, nail biting and gauging, and insertion of objects in orifices in Smith Magenis Syndrome.
- Anxiety disorders seen in William's Syndrome present with different subtypes of anxiety disorder.
- Major sleep disturbance and catnaps in Smith Magenis Syndrome is related to an inverted melatonin circadian cycle
- Autistic spectrum disorder, intellectual disability and motor incoordination in Joubert's Syndrome: cerebellar (vermal) agenesis.

The behavioural phenotype can lead to the genetic diagnosis and the chromosomal abnormality will often only be suspected on clinical grounds, and not always the other way round.

Interesting Facts to Know!

1 After 66 years, The Spastic Centre has been re-named the Cerebral Palsy Alliance but they still provide outstanding services to families and people with Cerebral Palsy. -SMH 9th February 2011

2 $16.1 million has been provided for Home and Community Care (HACC) services across NSW. The program will now total more than $625 million. - Federal Minister for Health and Aging and NSW Minister for Aging and Disability Services 27th January 2011

3 The NSW Ombudsman recently completed a review of the implementation of ADHC's Aboriginal Policy framework and Consultation Strategy. Visit www.ombo.nsw.gov.au to read the Report on improving service delivery to Aboriginal people with a Disability including 11 recommendations.

4 NSW Government has introduced legislation that will help people with disabilities cast a secret ballot in state elections using a new online and telephone voting system. iVoting is expected to be in place for the 2011 state election. Visit www.elections.nsw.gov.au

5 April is Autism Month and the 2nd of April is World Autism Day as declared by the United Nations. Visit www.worldautismawarenessday.org to register your event and download some resources. Be part of the big day!