Hypothesis: A specific pathway can be identified between genetic characteristics and behaviour profiles in Prader-Willi syndrome via cognitive, environmental and physiological mechanisms

ABSTRACT

Background

Behavioural phenotypes associated with genetic syndromes have been extensively investigated in order to generate rich descriptions of phenomenology, determine the degree of specificity of behaviours for a particular syndrome, and examine potential interactions between genetic predispositions for a behaviour and environmental influences. However, relationships between different aspects of behavioural phenotypes have been less frequently researched and although recent interest in potential cognitive phenotypes or endophenotypes has increased, these are frequently studied independently of the behavioural phenotypes.

Method

Taking Prader-Willi syndrome (PWS) as an example, we discuss evidence suggesting specific relationships between apparently distinct aspects of the PWS behavioural phenotype and relate these to specific endophenotypic characteristics.

Results

The framework we describe progresses through biological, cognitive, physiological and behavioural levels, to develop a pathway from genetic characteristics to behaviour, with scope for interaction with the environment at any stage.

Conclusions

We propose this multilevel approach as useful in setting out hypotheses in order to structure research that can more rapidly advance theory.

KEYWORDS:

Prader-Willi syndrome
Temper outbursts
Repetitive questions
Executive functioning
Cognitive phenotype
Behavioural phenotype

RUNNING HEAD:

Hypothesis: genes to behaviour in Prader-Willi syndrome

INTRODUCTION

Prader-Willi syndrome (PWS) is caused by the absence of expression of paternally derived (maternally imprinted) genes within a critical region (q11-q13) on chromosome 15. This occurs either through a paternal deletion (70% of individuals), maternal uniparental disomy (UPD: two copies of the maternal chromosome 15: 25%) or chromosomal translocations or defects of the imprinting centre (Boer et al., 2002). The physical PWS phenotype involves failure to thrive until approximately two years of age, followed by the onset of hyperphagia with a high risk for obesity in later life. Additionally, distinctive facial features, short stature, small hands and feet, hypogonadism and hypotonia are evident (Cassidy, 1997).

There appear to be a number of components of the PWS behavioural phenotype including excessive eating/ food seeking, specific repetitive and self injurious behaviours, temper outbursts, mood disturbance, daytime sleepiness/ under activity and lying/stealing/ 'disobedience' (Holland, Whittington & Butler et al., 2003). Cognitively there is a downward shift in IQ by about 40 points, but additionally there appears to be a profile of cognitive strengths and weaknesses that may include strengths in academic achievement and visual processing, and weaknesses in auditory processing, mathematical skills and short-term memory (e.g. Whittington et al., 2004).

ASSOCIATIONS BETWEEN ASPECTS OF THE BEHAVIOURAL PHENOTYPE

Factor analysis of questionnaire data has suggested an association between the PWS profile of repetitive behaviours (insistence on the sameness, preference for routine, repetitive questioning, hoarding, excessive cleaning and ordering) and temper outburst behaviour (Holland, Whittington & Butler et al., 2003). Our research has extended this apparent association between different aspects of the PWS behavioural phenotype using a bottom-up informant based interview approach to describing the nature of and contextual events surrounding the repetitive behaviours shown in children (aged 6-19 years) with PWS (REF 1, in press a).

Based on a sample of 46 individuals with PWS (deletion, UPD or clinical diagnosis), more than 70% of respondents reported a similar pattern. Children were reported to show a preference for predictability demonstrated by negative emotional behaviour when routines or expectations changed (e.g. when the school bus driver changed). Repetitive questioning was reported to focus predominantly on future events and occur more frequently following changes to routines or expectations. Changes to routines or expectations were likely to trigger temper outbursts, which were often described as including signs of physiological arousal such as increased salivation, increased breathing rate and a flushed facial appearance. While in line with the previous research discussed, importantly this method allowed us to generate a number of specific, testable hypotheses relating to potential associations between aspects of the PWS behavioural phenotype and the cognitive endophenotype that might underpin these associations.

The negative emotional behaviour that was related to changes to routines or expectations in children with PWS suggests that such changes were aversive to the children. The aversive nature of changes could cause the development of specific patterns of behaviour (questioning, temper outbursts) that allow escape from or avoidance of changes (Oliver, 1995). However, if the aversive nature of changes were the only factor causing these behaviours, we would expect the same behaviours to develop in any individuals for whom changes were aversive. Evidence from the interview study of REF 1 et al. (in press a) suggests that this is not the case. More than 70% of the carers of 33 boys (aged 9-19 years) with full mutation Fragile-X syndrome (FraX) also reported that negative emotional behaviour and repetitive questioning (also often about the future) followed changes to routines or expectations. This suggests that changes were aversive to the boys with FraX. However, the behaviour patterns following changes shown by boys with FraX were not the same as those shown by children with PWS. Temper outbursts were reported to follow changes in significantly less boys with FraX than children with PWS but overt displays of anxiety that included specific stereotypical and self-injurious behaviours were reported to follow changes in significantly more boys with FraX.

We therefore suggest that at least two pathways exist between genetic characteristics and behaviours in PWS. In the first pathway the genetic status of both PWS and FraX has a common effect on central nervous system development, ultimately resulting in changes being aversive to the individuals. This pathway would account for the negative emotional behaviour and repetitive questions shown by individuals with PWS and FraX. It is possible

that repetitive questioning develops due to the responses of the social environment to the questioning. However, it is also possible that questions are themselves reinforcing to the children due to the potential of the questions to increase or reinstate predictability. In support of this, children were reported to repeat questions over and over again despite being given the same answer repeatedly and knowing the answer themselves. This suggests that it is not obtaining an answer to a question that is reinforcing to a child, but the actual act of asking the question: perhaps constant verbal rehearsal of an upcoming event allows it to become predictable.

In the second pathway we suggest that the genetic status of PWS and FraX generates a propensity for the child to show a specific pattern of behaviour (temper outbursts in PWS and overt displays of anxiety in FraX) when stimuli are presented that are aversive to the child. This proposal of a gene-environment interaction is in line with previous research that considers environmental effects on genetically predisposed behaviour. For example in Angelman syndrome, social environmental effects on apparent genetic predispositions for laughing and smiling behaviour have been reported (Oliver, et al., 2002) and laughing and smiling has been shown to affect the behaviour of others (Oliver et al., 2007). Therefore, we would expect that any stimuli (not only changes) that are aversive to individuals with PWS or FraX could potentially trigger a temper outburst or display of anxiety. In support of this, overt displays of anxiety have been reported to be triggered in social situations in individuals with FraX when the individuals are thought to be in a physiologically aroused state (Hall et al., 2006).

THE ENDOPHENOTYPE ASSOCIATED WITH THE PWS BEHAVIOURAL PHENOTYPE

Perhaps one of the most important questions arising from the discussion above is why changes to routines or expectations are aversive to children with PWS and FraX. From a purely operant learning theory perspective, this question is difficult to answer as the inherent variable nature of changes mean that they can not be consistently associated with any primary reinforcing or punishing stimuli. However, a cognitive level within the behaviour model would have the potential to provide an explanation. The cognitive level must include deficiency in a cognitive capacity in both individuals with PWS and FraX so that changes would place a particularly high load on these individuals' cognitive resources.

Individuals with PWS and FraX both show intellectual disability so it could be suggested that changes are found to be aversive because they place a high demand on general cognitive resources. However, this would lead to the expectation that changes to routines and expectations would be more aversive to individuals with a greater degree of intellectual disability, which does not appear to be case. For example, a study comparing repetitive behaviour across individuals with a number of different genetic syndromes showed that individuals with syndromes associated with a greater degree of intellectual disability than that shown in PWS and FraX showed less preference for routine (Moss et al., in press). The shared cognitive deficiency in individuals with PWS and FraX associated with the resistance to change must therefore be in a more specific cognitive capacity or set of capacities. This fits in well with autism research. High functioning individuals with autism

show greater levels of preference for routine than individuals with autism and intellectual disability who show more stereotypical movement repetitive behaviour. It has been suggested that repetitive behaviour in autism is associated with deficits in executive functioning (Turner, 1999).

We investigated executive functioning (highest level cognitive processes that allow the control and regulation of behaviour) in 28 children (aged 6-19 years) with PWS deletion and 28 boys (aged 9-19 years) with full mutation FraX (REF 2, in press b). Children with PWS and boys with FraX showed different patterns of relative strengths and weaknesses in a number of specific executive capacities that were measured. However, both individuals with PWS and those with FraX showed a deficit in task-set reconfiguration, an aspect of task switching. This finding was in line with previous research in individuals with FraX (Wilding et al., 2001). Task switching involves switching from responding to stimuli based on one set of criteria (one cognitive-set) to responding to the same stimuli based on a different set of criteria (a different cognitive-set). Importantly, this finding fulfils our criteria for a shared deficit in a specific cognitive capacity in both individuals with PWS and FraX. A change in routine or expectation would force individuals to switch to a different way of thinking about the same stimuli and thus place a demand on this task switching capacity.

If a deficit in task switching in individuals with PWS and FraX does underlie the aversive state that is experienced following changes to routines or expectations, then we would expect a relationship to exist between the task switching deficit and the preference for predictability. In support of this prediction, we showed that a standardised switch cost

score was significantly positively correlated with informant report scores of preference for routine and predictability in children with PWS and FraX, but not with other classes of repetitive behaviour (REF 2 et al., in review). This suggests that children who showed increased problems with task switching also showed a higher level of preference for routine and predictability. We therefore propose that a common effect of genetic status in both PWS and FraX affects central nervous system development in a way that results in a cognitive endophenotype that includes a specific deficit in task switching. In an environment in which unexpected changes occur (predictability decreases) the deficit in task switching results in a particularly high load being placed on the child's cognitive resources. It is the high cognitive load that we propose causes changes to be aversive to the children.

A HYPOTHETICAL MODEL OF SPECIFIC BEHAVIOURS IN PWS

Figure 1 (using the conventions outlined by Morton, 2004) shows the hypothetical model that we propose detailing specific pathways between genetic character and behaviour in PWS via intermediate stages. This representation is useful in highlighting the hypotheses that arise from the discussion above, how these hypotheses are interrelated and how they could be immediately tested. Areas that require further investigation before specific hypotheses can be generated can also be identified.

[Figure 1]

The biological level in the model depicts the effect of genetic status on the development of the brain and central nervous system with the assumption of an influence of genetic abnormality on neurodevelopment. The literature on task switching in typically developing individuals supports an association between task switching and neural activity in areas of the prefrontal, anterior cingulate and parietal cortices (Derfuss et al., 2005; Wager et al., 2004). *Therefore we hypothesise that neural abnormalities in these areas may underlie the specific task switching deficit in PWS.* This hypothesis could readily be tested using neuroimaging techniques such as MRI and fMRI during task switching.

An additional proposed effect on central nervous system development accounts for the propensity of individuals with PWS to show temper outbursts when in an aversive state. In light of the discussion above and given the particularly high prevalence of temper outbursts in individuals with PWS (e.g. Holland, Whittington & Butler et al., 2003), this pattern of emotional deregulation may be specific to PWS. *Thus, we hypothesise that individuals with PWS show temper outbursts when in an aversive state and are more likely to show temper outbursts than individuals without PWS.* It is also possible that this emotional deregulation involves compromised arousal modulation. In this respect, the threshold level of arousal that can be reached before resultant behaviour is displayed may be lowered in PWS. Thus, individuals with PWS may be more likely to react when in an aversive state *and* this reaction may be more likely to encompass a temper outburst. Although hormonal abnormalities in regulatory systems have been reported with reference to the impaired satiety and excessive eating in PWS (e.g. Holland, Whittington & Hinton, 2003), to date there has been little investigation of the biological factors that could underpin the apparent

emotional deregulation. These issues would be exciting avenues for future research with implications for intervention.

It is necessary to consider the reported differences in behavioural and cognitive characteristics between individuals with different genetic subtypes of PWS (e.g. deletion versus UPD; Whittington et al., 2004). It is possible that the emotion deregulation is specific to individuals with a particular genetic mechanism associated with PWS or alternatively, that emotion deregulation is expressed differently in individuals with different genetic characteristics. Investigating these issues would assist in the study of pathways between particular genes and behaviours.

The cognitive level in the model details the endophenotype that includes the specific deficit in task switching. Importantly, the environment must interact with this endophenotypic characteristic to produce a behavioural outcome. *We hypothesise that decreases in predictability in the environment of an individual with PWS (e.g. unexpected changes to routines) produce a high cognitive demand due to the specific deficit that the individuals show in task switching.* This hypothesis could be tested by comparing groups of individuals with PWS who show relatively high verses low levels of deficit in task switching and measuring their performance on cognitive tasks while manipulating the level of predictability in an experimentally controlled environment. For support of the hypothesis, unexpected changes should cause a reduction in performance on cognitive tasks that is greatest for the high switching deficit group.

On a physiological level we hypothesise that this cognitive demand produces a state of arousal, which is aversive for the individual. Laboratory challenge studies have shown that cognitive demands can produce physiological arousal in the typically developing population (e.g. McCann et al., 1993). Numerous studies have associated physiological arousal with underlying emotional states such as fear and anxiety (e.g. Hofmann et al., 2006). Measuring physiological arousal whilst placing differing demands on individuals' task switching capacities or whilst the predictability of the individuals' environments is manipulated would allow direct tests of this hypothesis.

As discussed above, the proposed pathway between unexpected changes in the environment and the aversive, physiologically aroused state produced in individuals with PWS via a specific cognitive demand cannot be specific to individuals with PWS. Given our findings in boys with FraX and reports of executive dysfunction and preference for routine in individuals with autism, one possibility is that unexpected changes will be particularly aversive to *any* individuals who show deficits in task switching. There is some evidence to suggest that switching ability in typically developing children is associated with repetitive behaviour (Pietrefesa & Evans, 2007), but further specific investigation of task switching and preference for predictability in other groups of individuals would be necessary to address this issue.

The behavioural level in the model shows the pathway between the aversive, physiologically aroused state in individuals with PWS and the resultant repetitive questions or temper outbursts. However, the model must provide scope to explain why changes in

routine or expectations are not always followed by behaviours in individuals with PWS, why sometimes questions and at other times temper outbursts are triggered, and why different individuals may show different frequencies of these behaviours. We propose that the demand placed on the individual's cognitive switching capacity by a change in the environment may or may not exceed the level of cognitive resources available to the individual. In some situations the individual would be able to cope with the change and the change would be therefore less aversive. It is in these situations that children are likely to ask questions to increase predictability, possibly by processing the attention switching demand via a different cognitive route. *Thus, we hypothesise that if individuals with PWS are prevented from asking questions following a change, they will become more physiologically aroused.*

In other situations the individual with PWS will not have the cognitive resources necessary to cope with the change, the change will be more aversive and a temper outburst will occur. *We hypothesise that temper outbursts will be more likely to be shown by individuals with PWS following changes that place a high versus low demand on the individuals' cognitive resources.* By investigating cognitive task performance in individuals with PWS following different changes to the environment, it would be possible to assess which properties of changes increase the resultant cognitive demand and so test the behavioural effects of changes that result in varying levels of demand on cognitive resources.

These hypotheses relating to the behavioural level in the model would explain why changes in routine or expectations are not always followed by temper outbursts and why behaviour

varies across individuals with PWS. Even in individuals who show equal deficits in task switching, different individuals may have different levels of cognitive resources available and may be able to cope effectively with different levels of cognitive demand. Anecdotally, parents who report very few problems associated with changes in routine, report deliberately varying their child's environment to prevent routines from developing from an early age, which may have led to early acquisition of the cognitive skills necessary to deal with changes. This would have important implications in terms of potential for cognitive training strategies that could have positive influence on behaviour.

Finally, the hypothetical model we have presented allows for individuals with PWS showing repetitive questions and temper outbursts, to interact with the social environment within a mutual reinforcement framework involving carers. This potential interaction is important to consider because regardless of the underlying pathway to a behaviour, its immediate consequences could cause it to function in a distinct way for any particular individual. The maintenance and development of challenging behaviour via social contingencies has been consistently demonstrated in the literature (e.g. Iwata et al., 1982).

It is important to note that the hypothetical model that has been presented depicts a single snapshot of mechanisms, which exist within a developmental framework. Although 'cognitive deficits' have been discussed, the way in which these particular cognitive processes develop in individuals with PWS has not been described and most of the evidence discussed relates to children. Advantages have been highlighted with respect to the study of the developmental trajectories of cognitive capacities within

neurodevelopmental disorders (Karmiloff-Smith et al., 2004; Thomas et al., in press) and this perspective would be particularly useful within the present context given the potential implications of findings based on this approach, on cognitive intervention strategies. Thus, the model depicted in Figure 1 may be more informative if a time axis were placed perpendicular to the plane of the model in order to emphasise the importance of investigating the hypotheses drawn from the model from a developmental perspective.

The hypothetical model we have presented integrates areas of relative knowledge with phenomena that have not previously been investigated. In this way we were able to build a comprehensive model that identifies important influences, without necessarily having knowledge of the specific details. This enabled the generation of multiple testable hypotheses within a framework that gives comparative weight to each of these hypotheses. Importantly therefore, this hypothetical model should be able to promote future research in a structured way that will allow theory to advance relatively quickly.

REFERENCES

Boer, H, Holland, A. J., Whittington, J. E., Butler, J., Webb, T. & Clarke, D. (2002). Psychotic illness in people with Prader-Willi syndrome due to chromosome 15 maternal uniparental disomy. *The Lancet*, *359*, 135-136.

Cassidy, S. B. (1997). Prader-Willi syndrome. *Journal of Medical Genetics*, *34*, 917-923.

Derfuss, J., Brass, M., Neumann, J., & von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Human Brain Mapping, 25,* 22-34.

Hall, S, DeBernardis, M. & Reiss, A. (2006). Social escape behaviours in children with Fragile-X syndrome. *Journal of Autism and Developmental Disorders*, *36*, 935-947.

Hofmann, S., G., Moscovitch, D., A. & Kim, H. (2006). Autonomic correlates of social anxiety and embarrassment in shy and non-shy individuals. *International Journal of Psychophysiology, 61*, 134–142.

Holland, A. J., Whittington, J. E., Butler, J., Webb, T., Boer, H. & Clarke, D. (2003). Behavioral phenotypes associated with specific genetic disorders: Evidence from a population-based study of people with Prader-Willi syndrome. *Psychological Medicine, 33,* 141-153.

Holland, A., Whittington, J. & Hinton, E. (2003). The paradox of Prader-Willi syndrome: a genetic model of starvation. *The Lancet, 362,* 989-991.

Iwata, B., A., Dorsey, M., F., Slifer, K., J., Bauman, K., E. & Richman, G., S. (1982). Toward a Functional Analysis of Self Injury. *Analysis and Intervention in Developmental Disabilities, 2,* 3-20.

Karmiloff-Smith, A., Thomas, M., Annaz, D., Humphreys, K., Ewing, S., Brace, N. et al. (2004). Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories. *Journal of Child Psychology and Psychiatry, 45,* 1258-1274.

McCann, B., S, Carter, J., Vaughan, M., Raskind, M., Wilkinson, C., W. & Veith, R., C. (1993). Cardiovascular and neuroendocrine responses to extended laboratory challenge. *Psychosomatic Medicine, 55,* 497-504.

Morton, J. (2004). Representing causal relationships: Technical and formal considerations. Understanding Developmental Disorders. Chapter 3, *34-66.* Blackwell Publishing, Oxford, UK.

Moss, J., Oliver, C., Arron, K., Burbidge, C. & Berg, K. (in press). The Prevalence and Phenomenology of Repetitive Behaviour in Genetic Syndromes. *Journal of Autism and Developmental Disorders.*

Oliver, C. (1995). Annotation: Self-injurious behaviour in children with learning disabilities: Recent advances in assessment and intervention. *Journal of Child Psychology and Psychiatry, 36,* 909-927.

Oliver, C., Demetriades, L. & Hall, S. (2002). Effects of environmental events on smiling and laughing behaviour in Angelman Syndrome. *American Journal on Mental Retardation, 107*, 194-200.

Oliver, C., Horsler, K., Berg, K., Bellamy, G., Dick, K., & Griffiths, E. (2007). Genomic imprinting and the expression of affect in Angelman syndrome: what's in the smile? *Journal of Child Psychology and Psychiatry, 48,* 571-579.

Pietrefesa, A. S. & Evans, D. W. (2007). Affective and neuropsychological correlates of

children's rituals and compulsive-like behaviors: Continuities and discontinuities with obsessive-compulsive disorder. *Brain and Cognition, 65,* 36-46.

Thomas, M. S. C., Annaz, D., Ansari, D., Serif, G., Jarrold, C., & Karmiloff-Smith, A. (in press).The use of developmental trajectories in studying developmental disorders. *Journal of Speech, Language, and Hearing Research.*

Turner, M. (1999). Annotation: Repetitive behaviour in autism: A review of psychological research. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 40,* 839-849.

Wager, T. D., Jonides, J., & Reading, S. (2004). Neuroimaging studies of shifting attention: A meta-analysis. Neuroimage, *22*, 1679-1693.

Whittington, J., Holland, A., Webb, T., Butler, J. Clarke, D. & Boer, H. (2004). Academic underachievement by people with Prader-Willi syndrome. *Journal of Intellectual Disability Research, 48,* 188-200.

Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia, 40,* 1343-1349.

REF 1. (in press a). Associations between repetitive questioning, resistance to change, temper outbursts and anxiety in Prader-Willi and Fragile-X syndromes. *Journal of Intellectual Disability Research.*

REF 2. (in press b). Task switching deficits and repetitive behaviour in genetic neurodevelopmental disorders: Data from children with Prader-Willi syndrome chromosome 15 q11-q13 deletion and boys with Fragile-X syndrome. *Cognitive Neuropsychology.*

Figure 1. A hypothetical model of how the genetic character shown in PWS may be associated with endophenotypic characteristics which, via environmental interaction could result in behavioural phenotypic behaviours. The model was constructed following the conventions described by Morton (2004). The symbol "&" identifies points at which two factors (e.g. cognitive and environmental) must interact to cause a particular outcome.